

The Impact of Lifetime ADHD on Neuropsychological Functioning in Young Adults with
Bipolar Disorder: A Comparison of Bipolar Disorder with and without Childhood ADHD,
ADHD, and Control Groups.

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ABSTRACT

Almost all neuropsychological studies of adult bipolar disorder (BP) have failed to control for the established cognitive effects of attention deficit hyperactivity disorder (ADHD), and often other covariates. ADHD comorbidity in BP is common, and has already been shown to significantly worsen the clinical presentation of BP. This study of young adults (16 - 34 years) aimed to establish whether ADHD and BP with childhood ADHD groups had more impaired cognitive profiles (after controlling for numerous covariates) relative to BP without childhood ADHD and control groups. Using recognised structured and semi-structured clinical interviews and symptom rating scales, BP with ($n = 18$) or without ($n = 66$) childhood ADHD groups were recruited from a therapy study, and ADHD ($n = 27$) and control ($n = 26$) groups were recruited from the community. Participants completed tests (some from the Cambridge Neuropsychological Test Automated Battery) of executive functioning, memory, attention and psychomotor speed. MANCOVA results for cognitive performance indicated that the BP with childhood ADHD group did not differ significantly from the other three groups (except on a test of visual object memory, where it outperformed the ADHD group). The ADHD group was impaired relative to the BP without childhood ADHD and control groups on measures of verbal and visual memory. It was also more impaired than controls on a measure of attention. The BP without childhood ADHD group had visual memory and attention difficulties relative to controls. Compared to BP (controlling for ADHD), ADHD is associated with a more diverse range of cognitive impairment. Nevertheless, individuals with BP may independently demonstrate memory and attention difficulties which have the potential to interfere with treatment and day-to-day functioning.

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Most of the data in this study that pertains to bipolar disorder has come from a large clinical treatment trial (Psychotherapy for Bipolar Disorder Study) conducted by two of my supervisors (Professor Joyce and Dr Carter) as well as Dr Stephanie Moor, Associate Professor Marie Crowe, Dr Jane O'Malley, Dr Maree Inder, Robyn Abbott, Andrea Bartram, and Professor Martin Kennedy. I was one of three psychometricians that administered cognitive tests for this greater study. The treatment trial was run through the University of Otago at the Clinical Research Unit, Department of Psychological Medicine, Christchurch School of Medicine and Health Sciences. I am indebted to each of the investigators from this larger study who gave their time, commitment and hard work over several years. I would also like to extend my thanks to all the staff at the Clinical Research Unit for allowing me to use their psychometric testing equipment and interview rooms. In particular, I would like to acknowledge Associate Professor Chris Frampton, a biostatistician within the unit, who assisted me to undertake all the statistical analyses described in this thesis.

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PUBLICATIONS

The following has arisen directly from work completed as part of this thesis:

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CHAPTER 1: INTRODUCTION.

Overview of Bipolar Disorder.

According to the "Global Burden of Disease" study, commissioned by the World Health Organisation and the World Bank, bipolar disorder (BP) is the twelfth-ranked cause of disability in the world (Mathers, Boerma, & Fat, 2008). In explaining his own experience of BP, the renowned poet, Spike Milligan, explained: "I'm unbalanced. I'm not a normal person, and that's a very hard thing to have placed upon you in life" (Dixon, 2002, para.10).

Classification of bipolar disorder. The two foremost diagnostic systems employed to diagnose the bipolar disorders (BP) are the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR) (American Psychiatric Association, 2000) and the International Classification of Diseases (ICD-10) (World Health Organization, 1992). Although operational criteria are closely similar in DSM-IV-TR and ICD-10, the former is the most widely used classification system internationally, and the system used in New Zealand. The DSM-IV-TR (2000) assumes that each mental disorder is characterised by a unique constellation of symptoms which are associated with significant levels of current distress and functional impairment. In the DSM-IV-TR (2000), the bipolar disorders are subsumed within the more general category of Mood Disorders. The Mood Disorders section also includes diagnostic criteria for three forms of depressive disorder (i.e., Major Depressive Disorder, Dysthymic Disorder, and Depressive Disorder Not Otherwise Specified) and two additional mood disorders based on aetiology: Mood Disorder Due to a General Medical Condition, and Substance-Induced Mood Disorder. According to the DSM-IV-TR (2000), the bipolar disorders can be sub-divided into four distinct syndromes: Bipolar I Disorder (BPI), Bipolar II Disorder (BP II), Cyclothymic Disorder, and Bipolar Disorder Not Otherwise Specified. The bipolar disorders require the presence (or history) of manic episodes, either

hypomanic episodes or mixed episodes, and, typically, the presence (or history) of major depressive episodes.

To better understand the four bipolar disorder syndromes, consideration will first be given to each type of mood episode. To meet criteria for a manic episode, a person must have experienced a state of elevated or irritable mood, lasting for at least one week, or less if hospitalisation is required. During this distinct period of abnormal mood, an individual must have experienced at least three additional symptoms (four if the mood is only irritable): (1) inflated self-esteem or grandiosity; (2) decreased need for sleep; (3) more talkative than usual or pressure to keep talking; (4) flight of ideas or subjective experience that thoughts are racing; (5) distractibility; (6) increase in goal-directed activity or psychomotor agitation; (7) excessive involvement in pleasurable activities that have a high potential for painful consequences. The diagnostic criteria for a hypomanic episode also require that a distinct period of elevated or irritable mood be present, as well as at least three of the aforementioned symptoms (four if the mood is only irritable). The difference is that a shorter duration of mood instability is required (at least four days), and there must be an absence of hospitalisation during this time. For a mixed episode, an individual must have met the diagnostic criteria for a manic episode and for a major depressive episode (except for duration) (see below) nearly every day during a one-week period.

To meet criteria for a major depressive episode (MDE), an individual must have experienced five or more of the following symptoms for at least two weeks at a level that differed from previous functioning. At least one of the symptoms must be either (1) depressed mood most of the day, nearly every day; or (2) markedly diminished interest or pleasure in all, or almost all activities most of the day, nearly every day. Other possible symptoms include: (3) significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day; (4) insomnia or hypersomnia nearly every day; (5) psychomotor agitation

or retardation nearly every day; (6) fatigue or loss of energy nearly every day; (7) feelings of worthlessness or excessive or inappropriate guilt nearly every day; (8) diminished ability to think or concentrate, or indecisiveness, nearly every day; (9) recurrent thoughts of death, recurrent suicidal ideation without a specific plan or suicide attempt or a specific plan for committing suicide.

According to the DSM-IV-TR (2000), Bipolar I Disorder (BPI) is characterised by one or more manic or mixed episodes usually accompanied by major depressive episodes. Bipolar II disorder (BPII) is characterised by one or more major depressive episodes accompanied by at least one hypomanic episode. Both BPI and BPII can be further classified according to the degree of severity, content of psychotic features, level of remission, and longitudinal course. Cyclothymic disorder is characterised by at least 2 years of numerous periods of hypomanic symptoms that do not meet criteria for a manic episode and numerous periods of depressive symptoms that do not meet criteria for a MDE. Finally, a bipolar disorder not otherwise specified category is included in the DSM-IV-TR for disorders with bipolar features that do not meet criteria for any specific bipolar disorder.

Prevalence of bipolar disorder. A number of cross-sectional epidemiological studies have reported on the prevalence of BP. While some report only on BPI (Grant et al., 2005; Kessler, Rubinow, Holmes, Abelson, & Zhao, 1997; Weissman et al., 1996; Wells, Bushnell, Hornblow, Joyce, & Oakley-Browne, 1989), others include both BPI and BPII (Mitchell, Slade, & Andrews, 2004; Szadoczky, Papp, Vitrai, Rihmer, & Furedi, 1998) or even a broad definition of bipolar spectrum disorder (Kessler et al., 2005; Oakley-Browne, Wells, Scott, & McGee, (2006). The lifetime prevalence is approximately 1% for BPI and 1% for BPII and up to 5% when including all bipolar spectrum disorders. A meta-analysis of epidemiological studies detected a prevalence rate of 1.8% for paediatric bipolar spectrum disorders. For New Zealand in particular, a national mental health survey conducted during 2003 and 2004 found

that the lifetime prevalence for BPI was 1.0%, whereas the lifetime prevalence for BPPII was 0.7% (Wells, McGee, Scott, & Oakley-Browne, 2010). In an analysis of these results which also considered the prevalence of “sub threshold” BP, Maori were shown to be particularly at risk for developing BP symptomatology, with a lifetime prevalence of BP (based on BPI and BPPII statistics) of 8.3% (Baxter, Kingi, Tapsell, Durie, & McGee, 2006). Maori were also 2.4 times more likely to be hospitalised for BP than non-Maori (Baxter, 2007).

Comorbidity and its impact on bipolar disorder. Comorbidity has been broadly defined as the simultaneous presence in an individual of two or more mental or physical illnesses, disorders or diseases (Valderas, Starfield, Sibbald, Salisbury, & Roland, 2009). Psychiatric comorbidity in BP is the “rule rather than the exception” and, based on the literature, it can significantly contribute to worse clinical as well as functional outcomes. A later section (The clinical impact of ADHD comorbidity on BP) will consider the significant impact that ADHD comorbidity can have on BP. In a review by Krishnan (2005), the majority (approximately 50 to 70%) of individuals who had BPI or BPPII, of all ages and both genders, had at least one lifetime comorbid psychiatric disorder. Comorbid anxiety disorders are particularly common in BP with lifetime prevalence rates ranging from 28 to 63% for BP outpatients (Grabski, Dudek, Datka, Maczka, & Zieba, 2008; Judd & Akiskal, 2003; McElroy et al., 2001; Simon et al., 2004; Suppes et al., 2001). Comorbid social phobia (mean rate of 47%) and posttraumatic stress disorder (mean rate of 39%) are particularly common (Krishnan, 2005), and, in general, anxiety disorders have been shown to predict a poorer course of BP, including a higher likelihood of rapid cycling (Coryell, Endicott, & Keller, 1992; Kupfer, 2005), more pharmacologically induced hypomanic episodes (Masi et al., 2001), and more suicidal ideation as well as suicide attempts (Freeman, Freeman, & McElroy, 2002).

Comorbid substance use disorders also present frequently in BP with lifetime prevalence rates of 42 to 69% reported in BP outpatients (Goldberg, Garino, Leon, Kocsis, & Portera, 1999; Judd & Akiskal, 2003; McElroy et al., 2001; Regier et al., 1990; Sonne, Brady, & Morton, 1994; Suppes et al., 2001). Krishnan's (2005) review noted that comorbid alcohol abuse was the single most common comorbid psychiatric diagnosis in BP. In BP, substance use disorders have been associated with more severe mood symptomatology (Mazza et al., 2009), slower recovery from affective episodes (Baethge et al., 2005), higher rates of mixed episodes (Keller, Klerman, & Hirschfeld, 1986), rapid cycling (Keller et al., 1986), more compromised functional outcomes (Mazza et al., 2009; Strakowski et al., 1998), more suicide attempts (Fawcett, 1988), and more suicide (Potash et al., 2000; Vieta et al., 2000;). There are also elevated rates of comorbid eating disorders in BP outpatients, with lifetime prevalence rates ranging from 6 to 21% (McElroy et al., 2001; Suppes et al., 2001; Wildes, Marcus, & Fagiolini, 2008). Comorbid Axis II personality disorders have also been detected in BP with lifetime prevalence rates ranging between 29 to 40% (Brieger, Ehrt, & Marneros, 2003; George, Miklowitz, Richards, Simon, & Taylor, 2003; Kayl, Altshuler, Ventura, & Mintz, 2002; Preston, Merchant, Reimherr, Strong, & Hedg, 2004). In BP, studies have associated the presence of comorbid personality disorders with a greater severity of residual mood symptoms (George et al., 2003), lower rates of current employment (Kayl et al., 2002), the use of more psychiatric medications (Kayl et al., 2002), and a more frequent history of substance use disorders (Kayl et al., 2002; Preston et al., 2004).

Aetiology of bipolar disorder. Current theories of BP can be broadly categorized as 'genetic', 'biological', or 'psychosocial'. Generally, however, it is believed that BP is caused by a complex interaction of genetic, biological and psychosocial factors, known as the 'diathesis-stress' model (Lam, Jones, Bright, & Hayward, 1999; Nuechterlein & Dawson, 1984). This model, originally introduced to explain schizophrenia, attempts to explain how

genetic predisposition interacts with environmental stressors and life events to trigger disorders. According to the model, the greater the vulnerability through dispositional factors, the less stress that is required to trigger the event. The model has also been called the stress-vulnerability protection factors model. Many aetiological theories are based on particular genes or groups of genes as genetic studies show that BP is one of the most heritable of all mental disorders, with up to 80% concordance rates in monozygotic twins (Goodwin & Jamison, 2007). Linkage and association studies have identified several susceptibility loci and genes, though these do not appear to be specific to BP (for an overview, see Berrettini, 2001; Muller-Oerlinghausen, Berghofer, & Bauer, 2002).

Some biological theories have suggested that BP may be a function of hypothalamic-pituitary-adrenal (HPA) axis hyperactivity (Neves-Pereira et al., 2002). While some studies have correlated increased HPA activity with depression, mixed manic states, and occasionally classic manic episodes, there is also evidence that it may lead to compensatory abnormalities in neurotransmitter systems (Manji & Lenox, 2000; Pitchot, Herrera, & Ansseau, 2001).

Biological theories also suggest that BP may be a result of dysfunction to multiple neurotransmitter pathways and biological interactions. Several neurotransmitters, including norepinephrine, dopamine, glutamate, and γ -aminobutyric acid (GABA), have been implicated in BP to some degree, at least during symptomatic episodes (for an overview see Manji & Lenox, 2000). While biological theories suggest a role for neuroanatomical anomalies, the exact nature of these anomalies requires further clarification. However, the results of structural and functional imaging studies suggest that BP may be the result of a dysfunctional prefrontal–subcortical network interacting with a limbic network (for a review, see Strakowski, Delbello, & Adler, 2005). It has also been found that mania can be induced by sleep deprivation and a disruption of circadian rhythms (Wehr, Sack, & Rosenthal, 1987).

Less prominent are the psychosocial theories of aetiology. These models suggest that, to varying degrees, BP may be a reaction to stressful life events (Hammen & Gitlin, 1997), a dysregulation of self-esteem (Bentall, Kinderman, & Manson, 2005), and childhood trauma and abuse (Agid et al., 1999; Kendler, Neale, Kessler, Heath, & Eaves, 1992; Leverich et al., 2002).

Overview of ADHD.

Classification of ADHD. There are currently two terms employed for behavioural disorders of childhood characterised by the triad of symptoms of hyperactivity, inattention and impulsivity: attention deficit hyperactivity disorder (ADHD), used in DSM-IV-TR (2000) and hyperkinetic disorder, used in ICD-10 (1992). The main difference between the two sets of diagnostic criteria is that unlike the ICD-10 (1992), the DSM-IV-TR (2000) does not require that symptoms be present in each of the hyperactivity, inattention and impulsivity domains. This thesis will draw on the DSM-IV-TR (2000) classification of ADHD since there is a much larger evidence base relevant to our investigation for ADHD, than for hyperkinetic disorder. The DSM-IV-TR (2000) includes ADHD within the more general category of Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence. It bases the diagnosis of ADHD on the presence of developmentally inappropriate symptoms of inattention, impulsivity, and motor restlessness. ADHD symptoms must result in chronic, clinically significant impairment in at least two situations and be observed early in life (before age 7). Such symptoms must be present in the six months preceding a diagnostic assessment.

ADHD is subdivided into three primary diagnostic subtypes: “inattentive,” “hyperactive–impulsive,” and “combined” (reflecting a combination of the other two types). In the current categorical clinical view, these three subtypes belong to the same diagnostic entity. However,

some argue that the inattentive subtype is a distinct diagnostic disorder and not a subtype of ADHD (Barkley, DuPaul, & McMurray, 1990; Milich, Balentine, & Lynam, 2001). The ADHD Predominantly Inattentive Type requires that at least six of the following inattentive symptoms be present: (1) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities; (2) often has difficulty sustaining attention in tasks or play activities; (3) often does not seem to listen when spoken to directly; (4) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions); (5) often has difficulty organizing tasks and activities; (6) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework); (7) often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools); (8) is often easily distracted by extraneous stimuli or (9) is often forgetful in daily activities. For ADHD Predominantly Hyperactive-Impulsive Type, six (or more) hyperactive and/or impulsive symptoms must be present. The six hyperactive symptoms are: (1) often fidgets with hands or feet or squirms in seat; (2) often leaves seat in classroom or in other situations in which remaining seated is expected; (3) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness); (4) often has difficulty playing or engaging in leisure activities quietly; (5) is often "on the go" or often acts as if "driven by a motor"; and (6) often talks excessively. The three impulsivity symptoms include: (1) often blurts out answers before questions have been completed; (2) often has difficulty awaiting turn; (3) often interrupts or intrudes on others (e.g. butts into conversations or games). ADHD Combined Type requires the presence of at least 6 Predominantly Inattentive Type symptoms and 6 Predominantly Hyperactive-Impulsive Type symptoms. An ADHD not otherwise specified

subcategory is included in the DSM-IV-TR for disorders with ADHD features that do not meet criteria for any of the three primary ADHD subtypes.

Prevalence of ADHD. Adult ADHD prevalence rates are generally quite similar across studies, usually 4 to 5% (Fischer et al., 2007; Sobanski et al., 2007; Tamam, Karakus, & Ozpoyraz, 2008; Wingo & Ghaemi, 2007). Depending on the study, childhood prevalence of ADHD varies between 3 and 12% (Tamam et al., 2008; Wingo & Ghaemi, 2007). In New Zealand, the Christchurch Health and Development Study (CHDS) found that among New Zealanders aged 25 years, 9.3% had clinically significant levels of ADHD symptoms (Fergusson & Boden, 2008). However, studies conducted in New Zealand have yielded mixed results, with ADHD prevalence rates ranging from 2 to 6% in school-age children (Schaughency, McGee, Raja, Feehan, & Silva, 1994) and 4 to 7.5% in adolescents (Fergusson, Boden, & Horwood, 2010; Schaughency et al., 1994;).

Comorbidity and its clinical impact on ADHD. Before considering the specific rates of lifetime comorbidity in adults who have ADHD, it is important to acknowledge that it is mainly the ADHD syndrome per se, rather than additional psychiatric disorders, that accounts for poor clinical and functional outcomes (Miller, Nigg, & Faraone, 2007; Sobanski et al., 2007; Volk, Henderson, Neuman, & Todd, 2006). Like BP, comorbidity in ADHD is the “rule rather than the exception”. Research has found that almost 80% of ADHD adults had experienced at least one lifetime psychiatric comorbidity (Biederman et al., 1993; McGough et al., 2005; Murphy & Barkley, 1996;). Comorbid major depressive disorder appears to be particularly common in adult ADHD, with lifetime prevalence rates ranging from 24.4 to 55% (Biederman et al., 1993; Fischer et al., 2007; Hornig, 1998; Kessler et al., 2006; Miller et al., 2007; Sobanski et al., 2007). In adults, a history of lifetime comorbid depression has been associated with elevated rates of anxiety disorders and a higher demand for psychotherapy and pharmacological treatment (Fischer et al., 2007; Simon,

2003). In children, comorbidity has been associated with more severe ADHD symptomatology (Brunsvold, & Oepen, 2008). Comorbid anxiety disorders are also common in adult ADHD, with lifetime prevalence rates ranging from 17 to 47% (Kessler et al., 2006; Miller, 2007; Sobanski et al., 2007). In children, the presence of comorbid anxiety disorders has been associated with more attentional problems, school fears, and mood disorders, as well as lower levels of social competence (Bowen, Chavira, Bailey, Stein, & Stein, 2008). However, a large treatment study found that the presence of anxiety resulted in increased treatment response and a better prognosis (Jensen et al., 2001).

In adults with ADHD, the prevalence rates for lifetime comorbid oppositional defiance disorder and conduct disorder have been shown to range from 29 to 53% and 20 to 53%, respectively (Biederman et al., 1993). In studies of children, the presence of these comorbid disruptive conditions has been associated with the development of antisocial behaviour (Biederman et al., 1996; MacDonald & Achenbach, 1996), more severe ADHD symptomatology (Kuhne, Schachar, & Tannock, 1997), and poorer functional outcomes (Kuhne et al., 1997). Comorbid substance use disorders are also particularly common in adult ADHD, with lifetime prevalence rates ranging from 30 to 57% (Biederman et al., 1993; Miller et al., 2007; Sobanski et al., 2007; Sullivan & Rudnik-Levin, 2001). In adult ADHD, comorbid substance use disorders are associated with higher rates of psychiatric comorbidity, especially mood and anxiety disorders (Wilens, Faraone, & Biederman, 2004). Despite a lack of research, the presence of lifetime learning disorders also appears to be particularly common (67.5%) among ADHD populations (McGillivray & Baker, 2009). In children, the presence of learning disorder comorbidity in ADHD has been linked to poor cognitive, academic, and behavioural development (Church, Lewis, & Batshaw, 1997; Pisecco, Baker, Silva, & Brooke, 2001), as well as compromised social and emotional development (Bender & Wall, 1994; Biederman et al., 1993). Elevated lifetime rates of eating disorders (11.4%)

have also been detected in adults who have ADHD (Sobanski et al., 2007). The comorbidity of ADHD and Axis II personality disorders has rarely been studied. In a study which assessed Axis II comorbidity in ADHD adults, Cluster B (24.4%) and Cluster C (21.0%) disorders were more prevalent in the ADHD group (Miller et al., 2007). Other studies have detected elevated rates of comorbid antisocial personality disorder in 23% of young adults with ADHD (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993; Weiss, Hechtman, Milroy, & Perlman, 1985).

Aetiology of ADHD. The aetiology of ADHD has led to the development of a number of theoretical models that each point to different cognitive/neuropsychological deficits that are supposed to be the core deficits underlying ADHD (for an overview, see Nigg, 2005; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). These theories try to explain how biological factors (e.g., genes and brain processes) influence the overt behavioural symptoms that form the basis of diagnostics. However, until now, none of these theories has been able to provide a full explanation of all symptoms. In what follows, the three theories that have been most influential in the field will be briefly discussed. The Executive Dysfunction Theory (Barkley, 1997; Pennington & Ozonoff, 1996; Quay, 1997) has been the major model to guide research on ADHD over the past decade. Executive functioning is not a unitary construct, but rather an umbrella term for a broad range of “higher order” cognitive processes that enable a person to engage successfully in independent, goal-directed, self-serving behaviour (Lezak, 2004). These functions are mediated by the prefrontal cortex and other cortical (e.g., Anterior Cingulate Cortex; ACC) and subcortical (e.g., cerebellum, thalamus, basal ganglia) neural systems that are closely linked to the frontal lobe (Casey, 2005; Middleton & Strick, 2001; Pennington & Ozonoff, 1996). Executive functions can include skills such as inhibition, working memory, and cognitive flexibility. According to Barkley (1997), the core deficit in ADHD is a response inhibition deficit, which causes

secondary deficits in other executive functions. The Executive Dysfunction Theory of ADHD is derived from the observation that frontal lesion patients also show behavioural symptoms of inattention and hyperactivity/impulsivity (Mattes, 1980; Pontius, 1973). In addition, brain circuitry underlying executive functions has also been found to be compromised in ADHD.

The Delay-Aversion Hypothesis represents a further psychological model of ADHD (Sonuga-Barke, 1994). This model suggests that cognitive deficits are a consequence of an underlying motivational style of wanting to escape or avoid delay. The model was later elaborated to a dual-pathway model (Sonuga-Barke, 2002) in which delay aversion and poor inhibitory control are independent co-existing characteristics of ADHD. The third influential theory is the State Regulation hypothesis (Sergeant, 2000; Sergeant & van der Meere, 1990; van der Meere, 2005), based on Sanders' (1983, 1998) cognitive-energetic model. According to this hypothesis, children with ADHD are characterized by a non-optimal energetic state which results in the disinhibition of motor responses. Children with ADHD are often under-activated and are not able to adjust their energetic state to the demands of certain cognitive tasks, possibly due to insufficient extra effort allocation. However, factors that influence this energetic state (e.g., event rate and motivation) can have a beneficial effect on their task performance (Johnson, Wiersema, & Kuntsi, 2009).

Although the aetiology of ADHD is not completely understood, several studies have supported its strong genetic nature (Albayrak, Friedel, Schimmelmann, Hinney, & Hebebrand, 2008; Buitelaar, 2005; Chamberlain, Robbins, & Sahakian, 2007; Gerlach, Deckert, Rothenberger, & Warnke, 2008). Current behavioural genetic studies estimate the heritability of ADHD to be about 76% (Faraone et al., 2005). Linkage and association studies have identified several susceptibility loci and genes (for an overview, see Sharp, McQuillin, & Gurling, 2009). Although the neurobiological origin of ADHD has been well recognized, its exact neurobiological profile has not been fully characterized yet. However, structural and

functional imaging studies consistently suggest that dysfunctions in fronto-subcortical pathways and imbalances in dopaminergic and noradrenergic systems are implicated in the origin of the core symptoms of the disorder (Biederman, 2005; Bush, Valera, & Seidman, 2005; Castellanos et al., 2002; Chamberlain et al., 2007; Durston, 2003; Gerlach et al., 2008).

The Clinical Significance of BP with Comorbid ADHD.

Prevalence of bipolar disorder with comorbid ADHD. It is the high prevalence of ADHD symptom histories in individuals who have BP which provides much of the impetus for this investigation into neuropsychological outcomes. In a review of the BP with comorbid ADHD literature, Klassen, Katzman, & Chokka (2010) concluded that ADHD was a prevalent yet poorly understood comorbidity in adult and child/adolescent BP. Interestingly, ADHD comorbidity in BP appears to be markedly higher in children/adolescents compared to adults. Indeed, a meta-analysis of seven child/adolescent studies detected that ADHD comorbidity in BP was present 68% of the time (Kowatch, Youngstrom, Danielyan, & Findling, 2005). This was consistent with the present study's review, which found that ADHD comorbidity in child/adolescent BP ranged from 38 to 100% (Borchardt & Berstein, 1995; Faraone et al., 1997; Geller, Warner, Williams, & Zimmerman, 1998; Geller et al., 2000; Masi et al., 2006; West et al., 1996; West, McElroy, Strakowski, Keck, & McConville, 1995; Wozniak et al., 1995). Although the rates of comorbid ADHD reported for adult BP are significantly lower than those reported for BP in the child/adolescent literature, they are still markedly higher than the 4 to 5% baseline prevalence rates which have been reported for adult ADHD in the general population. A review conducted by Wilens and Dodson (2004) detected an ADHD comorbidity rate in adult BP of approximately 15%. This was also broadly consistent with the present study's review, which detected rates of comorbid ADHD in adult BP that ranged from 4 to 16.3% (Jaideep, Reddy, & Srinath, 2006; Nierenberg et al., 2005; Ryden et al., 2009; Sachs, Baldassano, Truman, & Guille, 2000; Tamam et al., 2008;

Tamam, Tug˘lu, Karatas, & ˆOzcan, 2006). Some studies have failed to find any evidence of comorbid ADHD in adult BP, but in 9.5 to 18.2% of cases have still detected evidence of childhood ADHD (Ryden et al., 2009; Tamam et al., 2008; Tamam et al., 2006).

It is unclear why lifetime comorbid ADHD has been detected significantly less often in adult BP compared to child/adolescent BP. Indeed, a number of hypotheses have been put forth. First, there is evidence that a significant minority of children/adolescents who have ADHD naturally fail to meet the diagnostic criteria for the syndrome as adults. A meta-analysis of follow-up studies found that although estimates of persistence varied with how the diagnosis of ADHD was defined, 35% of children with ADHD failed to meet the diagnostic threshold for ADHD in adulthood (Faraone, Biederman, & Mick, 2006). However, the authors stated that it was unclear whether this age-dependent decline in symptoms reflected true remission or the developmental insensitivity of diagnostic criteria for the disorder (Faraone et al., 2006). Consistent with evidence of a decline in ADHD symptoms over time, Tamam et al. (2008) noted that the rate of ADHD comorbidity in BP decreases steadily as the studied population ages, with rates of ADHD comorbidity reducing from as high as 98% in a pre-pubertal manic group (Wozniak et al., 1995), to around 70% in early adolescence (West et al., 1995), and then to 30% in late adolescence (Geller et al., 1998). It has also been suggested that the reduced rates of comorbid ADHD in adult BP relative to child/adolescent BP may partially reflect a tendency toward underreporting of childhood-onset ADHD symptoms in adults. In a study by Mannuzza, Klein, Klein, Bessler, & Shrout (2002), 22% of adults who met criteria for ADHD as children failed to correctly recall their symptoms 16 years later.

The clinical impact of ADHD comorbidity on bipolar disorder. BP with a lifetime history of ADHD is associated with a particularly severe clinical profile characterised by an early onset of mood symptomatology, a greater frequency of mood episodes, multiple comorbidities, and a poor response to psychotropic medication. Given that the presence of

such variables may negatively affect cognitive functioning, the present study considers the extent to which the groups are matched on these variables. Such variables are included as covariates in analyses if they are differentially distributed between the groups. As demonstrated in a later section (The Clinical Impact of ADHD Comorbidity on Bipolar Disorder section), BP with a history of ADHD is also associated with poor functional outcomes. This study considers whether any impaired functional outcomes in this group are related to cognitive difficulties to a greater or lesser extent than for ADHD and/or BP without childhood ADHD groups. Some authors have suggested that BP with lifetime ADHD may represent a distinct BP phenotype (Faraone, Biederman, & Monuteaux, 2001; Ryden et al., 2009; Singh, DelBello, Kowatch, & Strakowski, 2006; Wilens et al., 2003). Alternatively, it may represent the interaction of two distinct illnesses (Biederman et al., 2008).

Earlier age of onset for bipolar disorder. In their review of the BP with comorbid ADHD literature, Klassen et al. (2010) concluded that the earlier age of BP onset was the “critical variable” that differentiated BP with lifetime ADHD from BP without lifetime ADHD. Indeed, the results of at least four studies have led to widespread acceptance of the idea that ADHD comorbidity is associated with early onset BP (Biederman, 2004; Faraone et al., 1997; Sachs et al., 2000; Tamam et al., 2008). Studies have shown that adults who have BP with a history of childhood ADHD but not current ADHD still demonstrate significantly lower ages of BP onset. In the study by Ryden et al. (2009), the mean age of BP onset for such a group was 16.6 compared to 23.4 for a BP-only group. In the Tamam et al. (2008) study, the mean age of BP onset for the BP-only group was 25.7, whereas it was 19.8 for the BP group that had childhood ADHD but not current ADHD. Not surprisingly, significantly lower ages of BP onset have also been demonstrated in BP groups that have current ADHD. In the Ryden et al. (2009) study, the mean age of BP onset for such a group was 18.2 compared to 23.4 for a BP-only group. In Tamam et al.’s (2008) study, it was 17.6 compared

to 25.7. In a large-scale study by Nierenberg et al. (2005), the onset of BP occurred approximately 5 years earlier in a BP with lifetime comorbid ADHD sample (at age 13.9). While Saches et al. (2000) found that ADHD was only present in those adults with BP who had an onset of BP before the age of 19 years, Wilens et al. (2003) reported that 60% of adults who had BP with comorbid ADHD had experienced BP onset as children or adolescents. According to Sachs et al. (2000), early onset BP could be a subtype with higher genetic loading and therefore increased vulnerability to the development of both early affective and non-affective psychopathology.

Greater frequency of mood episodes. There is evidence that the presence of lifetime ADHD can worsen the BP mood course. Studies have shown that adults who have BP with a history of childhood ADHD but not current ADHD still demonstrate significantly more mood episodes. In the study by Ryden et al. (2009), the mean number of mixed episodes for such a group was 15.4 compared to 3.6 for a BP-only group. In the Tamam et al. (2008) study, an adult BP group that had childhood ADHD but not current ADHD had greater rates of total episodes (6 compared to 3.9) and depressive episodes (2.5 compared to 1.2) relative to a BP-only group. Not surprisingly, greater rates of mood episodes have also been demonstrated in BP groups that have current ADHD. Tamam et al. (2008) found that a BP with current comorbid ADHD group had higher rates of total episodes (6.7 compared to 3.9) and depressive episodes (2.9 compared to 1.2) relative to a BP-only group. In the study by Ryden et al. (2009), the BP with current ADHD group had significantly greater rates of hypomanic episodes (15.4 compared to 3.6) and total episodes (33.4 compared to 13.4) compared to a BP-only group.

The Tamam et al. (2008) study noted that adults who had BP with current or childhood ADHD showed a greater number of total mood episodes than a BP-only group (the mean number of episodes were 6.7, 6.0, and 3.9, respectively), as well as a greater number of

depressive episodes (the mean number of depressive episodes were 2.9, 2.5, and 1.2, respectively) relative to the BP-only group. In the study by Nierenberg et al. (2005), the proportion of adults with more than 20 lifetime episodes of either mania or depression was significantly higher in BP adults with lifetime comorbid ADHD (40.7%), compared to BP adults without lifetime ADHD (29.6%). While 41.2% of those who had BP with lifetime ADHD had experienced 20 or more depressive episodes, this was the case for only 31.3% of BP adults without lifetime ADHD (Nierenberg et al., 2005). Nierenberg et al. (2005) also reported that adults who had BP with lifetime ADHD demonstrated shorter periods of wellness. Other studies have also reported a higher frequency of depressive episodes in individuals with BP and comorbid ADHD (4.3 compared to 0.5) (Tamam et al., 2006). A recent study found that rapid cycling was particularly common in children who had BP with comorbid ADHD compared to ADHD alone (Donfrancesco et al. 2010).

To be able to reliably detect differences in the frequency of mood episodes between individuals who have BP with and without lifetime ADHD, samples may need to consist of adults. Indeed, a study of children and young adolescents failed to detect differences in the rates of mood episodes between BP with and without comorbid ADHD groups (Geller et al., 2000). However, there is evidence that ADHD comorbidity can amplify the severity of BP symptomatology in children or adolescents. West et al. (1995) found that adolescents who had BP with comorbid ADHD demonstrated more severe mania symptomatology (as rated by the Young Mania Rating Scale). In the study by Biederman et al. (1996), children and adolescents who had ADHD with comorbid BP exhibited prominent prototypical symptoms of mania, with severe agitation and irritability, rather than euphoria, dominating the clinical picture. In a study of 274 children with ADHD, a particularly impairing form of irritability defined as “super-angry/grouchy/cranky” only presented when children demonstrated BP comorbidity (Mick, Spencer, Wozniak, & Biederman, 2005).

In an attempt to understand why ADHD may contribute to mood difficulties in BP, it has been suggested that consideration must be given to the high comorbidity rates between depression and ADHD (see Prevalence of Bipolar Disorder with Comorbid ADHD section) (Biederman, 2004; Pliszka, 1998). It is possible that adults with BP who have ADHD are generally less compliant to treatment (Tamam et al., 2006). Similarly, the nature of ADHD symptoms (i.e., inattention, lack of organization and forgetfulness) may compromise treatment adherence.

Multiple comorbidities. BP and comorbid ADHD can be associated with high rates of additional psychopathology, especially in adults. This is significant because additional psychopathology (e.g. anxiety disorders and alcohol/substance abuse/dependence) can significantly compromise the disease course and contribute to worse clinical as well as functional outcomes (see The Clinical Impact of ADHD Comorbidity on Bipolar Disorder section). In the study by Nierenberg et al. (2005), adults with BP who had a history of comorbid ADHD exhibited a greater number of additional comorbid psychiatric conditions, including several anxiety disorders (agoraphobia without panic disorder, social phobia, posttraumatic stress disorder, and generalized anxiety disorder), as well as alcohol and substance abuse and dependence. Indeed, the odds ratio of having these additional comorbid conditions was greater than two (Nierenberg et al., 2005). A study by Wilens et al. (2003) detected significantly higher rates of simple phobia and a trend towards higher rates of agoraphobia, alcohol dependence, conduct and antisocial disorders in a BP with comorbid ADHD group relative to a BP-only group. Tamam et al. (2008) found that 65% of adult participants diagnosed with co-occurring ADHD and BP presented a lifetime history of at least one anxiety disorder such as panic disorder and higher rates of alcohol abuse/dependence.

The findings of the child and adolescent literature are more disparate. Indeed, a study by Geller et al. (2000) reported that ADHD comorbidity did not impact significantly on rates of psychosis or of comorbid oppositional defiant disorder in children and early adolescents who had BP. Similarly, West et al. (1995) reported no differences between adolescents who had BP with or without ADHD in terms of psychosis, anxiety or depression. Nevertheless, Biederman et al. (1996) reported that children with ADHD who had comorbid BP demonstrated elevated rates of severe major depression, multiple anxiety disorders, psychosis, conduct disorder, and oppositional defiant disorder relative to non-BP ADHD probands. Indeed, the ADHD-BP comorbidity was associated with a higher mean number of comorbid disorders per child at both baseline and follow-up assessments (Biederman et al., 1996). In an earlier study, Wozniak et al. (1995) reported the same findings with a sample of 42 children who had ADHD and comorbid mania.

Poorer response to medication. The core symptoms of ADHD, inattention, hyperactivity, and impulsivity, have been shown to prevent individuals with BP from following their treatment regime, thereby increasing the tendency to develop new affective episodes (Pliszka, 1998; Tamam et al., 2006). A 2-year naturalistic follow-up study reported that youth with BP and comorbid ADHD had a relatively poor clinical outcome (65% recovery rate in 2 years) and for the 47% and 59% of youth receiving either an anti-manic or stimulant medication respectively, treatment was not predictive of recovery (Geller et al., 2002).

Poorer functional outcomes. There is some evidence that a BP subgroup is at risk for particularly poor functional outcomes (Martinez-Aran et al., 2000). It is possible that a history of ADHD symptoms may contribute to this impairment as BP coupled with ADHD is associated with considerably higher rates of functional impairment. There are a number of examples of impaired functional outcomes in adults who have BP and a history of ADHD

symptoms. The study by Ryden et al. (2009) has shown that adults who have BP with a history of childhood ADHD but not current ADHD still demonstrated significantly more interpersonal violence than a BP-only group. In the same study, a BP with current ADHD group also demonstrated both more interpersonal violence and more suicide attempts compared to the BP-only group (Ryden et al., 2009). While Nierenberg et al. (2005) reported that such adults exhibited lower education, a greater lifetime history of violence, suicide attempts, and legal problems, Wilens et al. (2003) reported that they also performed poorer on tests of global functioning (GAF). In a recent study of euthymic phase BP outpatients, comorbid ADHD predicted significantly lower social functioning and adaptation compared to individuals with BP who did not have lifetime ADHD (Sentissi et al., 2008).

Functional outcomes can also be more compromised in children and adolescents who have BP with comorbid ADHD, although the findings are more variable. Indeed, children with ADHD and comorbid BP or co-occurring manic symptoms have been reported to exhibit higher rates of psychiatric hospitalisation and lower scores on tests of global or social functioning relative to non-BP children with ADHD (Biederman et al., 1996; Galanter et al., 2005; Wozniak et al., 1995;). Nevertheless, West et al. (1995) reported that children who had ADHD with comorbid BP did not differ significantly from an ADHD sample with regard to the length of hospitalisation, or number of medications at discharge. Further, Geller et al. (2000) noted that the number of attempted suicides did not vary between children and early adolescents who had BP with or without ADHD. Galanter et al. (2005) replicated this finding with children who had ADHD with manic features.

The Contribution of Lifetime ADHD to Neuropsychological Functioning in Bipolar Disorder

BP with a lifetime history of comorbid ADHD may partially account for findings of severe clinical impairment in BP. As demonstrated in an earlier section (The Clinical Significance of BP with Comorbid ADHD), the contribution of ADHD to clinical difficulties in BP is unlikely to be a rare occurrence as ADHD comorbidity is particularly high in child/adolescent BP and is elevated in adult BP. In light of such findings, it is significant that BP is associated with a pattern of cognitive dysfunction that largely parallels that observed in ADHD. Like the other clinical difficulties mentioned above, the findings of neuropsychological impairment in BP may be partially an artefact of lifetime comorbid ADHD, given that almost all studies of adult BP have failed to control for the effects of lifetime ADHD. In this section, the potential contribution of lifetime ADHD to neuropsychological functioning in BP will be considered.

Executive functioning. The definition of executive function varies according to the specific skill identified, the academic discipline, and the author defining the skill (Hervey, Epstein, & Curry, 2004). As described earlier, executive functions can be defined as a collection of higher-order cognitive control processes that are necessary to guide goal-directed behaviour. It is plausible that ADHD contributes to executive dysfunction in BP, as comparable levels of executive function impairment tend to occur across both syndromes. ADHD is often characterized by underdeveloped behavioural inhibition, working memory, temporal organization, and regulation of emotions, which are traditionally ascribed to deficient executive functioning (Barkley, 1997). Indeed, several authors have proposed that symptoms of ADHD arise from a primary deficit in a specific executive function domain such as response inhibition, or working memory, or a more general weakness in executive control (Barkley 1997; Castellanos & Tannock, 2002; Pennington & Ozonoff 1996; Schachar, Mota, Logan, Tannock, & Klim, 2000). This hypothesis is based on the

observation that prefrontal lesions sometimes produce behavioral hyperactivity, distractibility, or impulsivity, as well as deficits on executive function tasks (Fuster, 1997; Stuss & Benson, 1986). However, the results of a recent meta-analysis which detected moderate effect sizes and lack of universality of executive dysfunction among individuals with ADHD suggest that executive function weaknesses are not a precondition for all cases of ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Instead, executive function difficulties appear to be one of several important weaknesses that comprise the overall neuropsychologic aetiology of ADHD (Willcutt et al., 2005).

Verbal fluency. The fluency of speech represents a cognitive function which is highly correlated with executive functioning and attention capacity (Lezak, 2004). It is typically indexed by the number of words produced, usually within a restricted category or in response to a stimulus, and within a given timeframe (Lezak, 2004). Two major categories of verbal fluency tasks can be distinguished, namely semantic category fluency (recitation of examples of a given category) and letter fluency (generating words beginning with a given initial letter) (Hurks et al., 2004). Meta-analytic research of adults with ADHD reported a large effect for category fluency (Hervey et al., 2004), although only one study was included, and medium effects for letter fluency (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Hervey et al., 2004). Smaller effects for both letter (Frazier, Demaree, & Youngstrom, 2004) and category fluency (Frazier et al., 2004; Pennington & Ozonoff, 1996) were demonstrated in meta-analyses of child/adolescent ADHD.

It is plausible that ADHD contributes to verbal fluency difficulties in BP, as comparable levels of impairment tend to occur across both syndromes. Unfortunately, there are no studies of BP that explicitly consider verbal fluency performance while controlling for the potential cognitive effects of lifetime comorbid ADHD. Meta-analytic research has detected medium (Kurtz & Gerraty, 2009) and large (Arts, Jabben, Krabbendam, & Van Os, 2008; Robinson et

al., 2006) effects for category fluency in euthymic phase adult BP. For letter fluency, meta-analytic research of adults has detected small (Arts et al., 2008; Bora, Yucel & Pantelis, 2009; Robinson et al., 2006; Torres, Boudreau, & Yatham, 2007) and medium (Kurtz & Gerraty, 2009; Mann-Wrobel, Carreno, & Dickinson, 2011) effects for euthymic phase BP, and medium and large effects for mixed/manic phase (Kurtz & Gerraty, 2009) and depressed phase (Kurtz & Gerraty, 2009) BP, respectively. There appear to be no controlled studies that have applied a test of verbal fluency to children/adolescents who have BP. There is, however, some indication that impairment may be evident on such a task. McClellan, Prezbindowski, Brieger, & McCurry (2004) found that children/adolescents with BP performed similarly to children/adolescents who had debilitating conditions associated with severe neurocognitive impairment, including schizophrenia.

Cognitive flexibility. Cognitive flexibility is an important executive function which enables one to shift a course of thought or action according to the demands of a situation (Lezak, 2004). In measuring cognitive flexibility, most studies have considered the total time taken to complete the Trail Making Test Part B (TMT-B) and/or the number of perseverative errors made on the Wisconsin Card Sorting Test (WCST). For adults with ADHD, meta-analytic research has reported a moderate effect for the TMT-B (Boonstra et al., 2005; Hervey et al., 2004) and a small effect for the WCST (Hervey et al., 2004).

It is plausible that ADHD partially accounts for reports of cognitive inflexibility in BP, as comparable levels of impairment tend to occur across both syndromes. Some studies have attempted to explicitly control for ADHD. In a study by Torralva et al. (2010), adults who had euthymic phase BP without lifetime comorbid ADHD failed to differ significantly from control groups on the TMT-B or the perseverative errors outcome measure of the WCST. Similarly, Rucklidge (2006) failed to detect significant differences between adolescents who had BP without lifetime ADHD or control groups on the Color Trails 2 test (a variant of the

TMT-B). Interestingly, Rucklidge (2006) did detect impaired performance on this measure in a BP with comorbid ADHD group relative to controls. Although the effect disappeared after controlling for IQ, it is still of interest, given that IQ is largely supported by executive functions. On the WCST, Doyle et al. (2005) failed to detect impairment among children/adolescents who had BP and controls after statistically controlling for ADHD.

Not every study has demonstrated that ADHD contributes significantly to cognitive flexibility. In a study by Dickstein et al. (2004), children who had euthymic/hypomanic phase BP performed significantly worse than controls on the CANTAB

Intradimensional/Extradimensional Shift test, a task which mirrors that of the WCST.

Although no significant differences were detected between BP with comorbid ADHD and BP without lifetime ADHD groups, it is significant that the subgroups were particularly small (of the BP group, 15 had ADHD comorbidity and 7 did not), as this may have made it difficult to detect an effect (Dickstein et al., 2004). Henin et al. (2007) also found that children/adolescents in a BP with comorbid ADHD group did not differ significantly from controls in terms of WCST perseverative errors. Such a finding reinforces the notion that ADHD symptom histories are likely to contribute to neuropsychological impairment in BP rather than account for it.

It is therefore unclear whether the undetected presence of ADHD may partially account for meta-analytic findings of small (Arts et al., 2007), medium (Kurtz & Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007), and large (Bora et al., 2009; Mann-Wrobel et al., 2011) effect sizes for adults who had euthymic phase BP on the TMT-B. Similarly, it is unclear whether ADHD contributed to meta-analytic findings of a medium effect for performance on the TMT-B among adults with BP who were experiencing a depressed or mixed/manic phase episode (Kurtz & Gerraty, 2009). Whether the presence of undetected lifetime comorbid ADHD can also partially account for the small (Arts et al., 2007) and

medium (Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011) meta-analytic effects which have been detected for adults who have euthymic phase BP on the WCST, or for a medium effect for depressed stage BP on the WCST, requires further research (Kurtz & Gerraty, 2009). Other than the four studies mentioned which controlled for ADHD, no other controlled studies appear to have assessed cognitive flexibility in child/adolescent BP.

Working memory. Working memory represents one's ability to attend to information, hold and mentally manipulate that information in short-term memory and formulate a response based on that information (Lezak, 2004). According to a three-component model of human working memory, first developed by Alan Baddeley and Graham Hitch in 1974, such measures are particularly sensitive to a central executive component, which is believed to facilitate the control and regulation of cognitive processes (Baddeley & Hitch, 1974).

Spatial working memory. According to Baddeley's model, the temporary storage and manipulation of spatial information is facilitated by a visuospatial sketchpad which is principally represented within the right hemisphere of the brain (Baddeley & Hitch, 1974). In ADHD, tasks that tap into spatial working memory, including the CANTAB Spatial Working Memory test, are associated with significantly higher levels of impairment relative to tasks like Digit Span Backwards, which implicate verbal working memory. This pattern of findings may arise because spatial working memory tasks tend to involve the right hemisphere, which has been implicated in ADHD (Giedd, Blumenthal, Molloy, & Castellanos, 2001).

Alternatively, it is possible that another disorder underlies the spatial WM weaknesses in ADHD. Approximately half of all children with ADHD may have motor difficulties consistent with developmental coordination disorder (Barkley et al., 1990; Piek, Pitcher, & Hay, 1999; Pitcher, Piek, & Hay, 2003). Developmental coordination disorder has been shown to be strongly associated with deficiencies in visuospatial processing (Wilson &

McKenzie, 1998). Studies conducted with adults have detected large effects for the CANTAB Spatial Working Memory test (SWM) in adult ADHD (Chamberlain et al., 2007; Dowson et al., 2004; McLean et al., 2004). In a meta-analysis by Martinussen, Hayden, Hogg-Johnson, & Tannock (2005), spatial working memory was associated with a large effect for childhood ADHD.

It is plausible that ADHD partially accounts for the inconsistent findings of spatial working memory impairment in BP. This seems particularly reasonable if one considers that behavioural disinhibition, a relatively frequently detected deficit in ADHD, has direct implications for both spatial and verbal working memory (Frazier et al., 2004). Given that ADHD during childhood/adolescence appears to be associated with poor SWM test performance, it is somewhat surprising that differences in SWM performance between child/adolescent euthymic phase BP (of whom 71% had lifetime ADHD) and control groups were non-significant in the only other study that attempted to control for ADHD (Dickstein et al., 2004). Although Dickstein et al. (2004) also failed to detect significant differences between BP with comorbid ADHD and BP without current comorbid ADHD subgroups, the small sample sizes of these subgroups may have made it difficult to detect significant effects. In the Dickstein et al. (2004) study, it is plausible that the absence of impairment may have been an artefact of the SWM outcome measure used. Given that within search errors are rarely detected in ADHD, it is possible that the total search error outcome measure (which collapses together within and between search errors) was not sensitive enough to detect impairment.

As discussed above, studies of adult BP which have failed to control for ADHD have detected a wide range of findings for measures of spatial working memory. Using the CANTAB Spatial Working Memory test, some studies have failed to detect differences in between search error rates when comparing controls to euthymic (Clark, Iversen, &

Goodwin, 2002), depressed (Braw et al., 2007; Roiser et al., 2009;), or manic/mixed (Badcock, Michiel, & Rock, 2005) phase BP groups. Other studies which failed to control for ADHD have detected elevated rates of between search errors in adults with euthymic (Barrett, Kelly, Bell, & King, 2008; Thompson et al., 2005) or manic/mixed (Clark, Iversen, & Goodwin, 2001; Sweeney, Kmiec, & Kupfer, 2000) phase BP relative to controls. This inconsistent pattern of results is also present for strategy scores on the CANTAB Spatial Working Memory test. Some research with adults has failed to detect significant differences in strategy scores between controls and euthymic (Clark et al., 2002), depressed (Sweeney et al., 2000), or mixed/manic (Badcock et al., 2005) phase BP samples. Nevertheless, other studies have detected significantly lower strategy scores in euthymic (Barrett et al., 2008) or mixed/manic (Sweeney et al., 2000) phase BP groups compared to controls. Other than the one study discussed above (Dickstein et al., 2004), no other controlled studies appear to have assessed spatial working memory in child/adolescent BP.

Verbal working memory. Baddeley's model suggests that auditory verbal information is entered into a phonological loop consisting of a phonological store for auditory memory traces that are subject to rapid decay, and an articulatory rehearsal component that can revive such memory traces. Although the composite score from the Digit Span subtest has been used to index verbal working memory in many neuropsychological studies, caution is warranted. Through summing performance across Digit Span Backwards, a test of verbal working memory, and Digits Span Forwards, a task more closely associated with short-term memory storage or attentional efficiency, the composite score can be misleading (Lezak, 2004). Hence, the proceeding review gives more weight to studies that employ Digit Span Backwards as the dependent variable. Meta-analytic research reports a small to medium effect for verbal working memory across adult ADHD samples as indexed by the Digit Span Backwards test (Boonstra et al. 2005). In children/adolescents who have ADHD, a meta-

analysis detected a moderate effect across a range of verbal working memory tasks (Martinussen et al., 2005).

It is also plausible that ADHD partially accounts for the variable findings of verbal working memory impairment in BP. As discussed above, behavioural disinhibition, which is a relatively frequently detected deficit in ADHD, also has direct implications for verbal working memory (Frazier et al., 2004). Several other studies have attempted to control for the effects of lifetime comorbid ADHD. In the study by Torralva et al. (2010), there were no significant differences between BP without ADHD and control groups on the DSB test. This result was broadly similar to the findings reported in studies of children/adolescents that controlled for ADHD and failed to detect significant differences between BP and control groups in terms of Digit Span composite scores (the sum of scores on Digit Span Forwards and Digit Span Backwards) (Doyle et al., 2005; Rucklidge, 2006). It was therefore somewhat surprising that Rucklidge (2006) also failed to detect a significantly lower composite score for the Digit Span test in a group of adolescents who had BP with comorbid ADHD.

Interestingly, studies that have controlled for ADHD have detected impairment in BP on other measures of verbal working memory. While Torralva et al. (2010) noted that adults with euthymic phase BP without ADHD performed worse than controls on the Letter-Number Sequencing test, two other studies (Doyle et al., 2005; Rucklidge, 2006) noted that children/adolescents with BP performed worse than controls on the Arithmetic subtest. Not surprisingly, Rucklidge (2006) also noted that a BP with comorbid ADHD group was also impaired relative to controls on the Arithmetic test.

In light of the previous review, it is still unclear whether the presence of lifetime comorbid ADHD can account for the variable meta-analytic findings of verbal working memory impairment that have been detected for BP. For euthymic phase adults who have BP, meta-analytic research has reported small (Arts et al., 2007), medium (Bora et al., 2009; Kurtz &

Gerraty, 2009; Mann-Wrobel et al., 2011; Torres et al., 2007;) and large (Robinson et al., 2006) effects for verbal working memory as indexed by the Digit Span Backwards test. Other than the two studies (Doyle et al., 2005; Rucklidge, 2006) which controlled for ADHD, only one other study has considered verbal working memory in child/adolescent BP. In this study by Robertson et al. (2003), which failed to control for comorbid ADHD, stable youth with BP did not exhibit deficits on the Digit Span Backwards test relative to controls or a unipolar depression sample.

Inhibition. Inhibition represents one's ability to inhibit or withhold one's actions (Boonstra et al., 2005). While Barkley (1997) has theorised that ADHD is largely the result of a core deficit in inhibition, the validity of such single cause theories has been strongly debated (see above). Findings of disinhibition in ADHD have varied depending on the types of measures that have been used. In adult meta-analytic studies, the total errors condition of the Matching Familiar Faces Test has been associated with small effects for adult ADHD (Hervey et al. 2004), whereas large effects for adult ADHD have been detected for reaction times on the stop-signal test (Hervey et al. 2004) and for errors on the Stroop Color Word test (Boonstra et al., 2005). For adult ADHD, meta-analytic research has detected small (Hervey et al. 2004) effects for commission errors on traditional continuous performance tests (CPTs), and moderate (Boonstra et al., 2005; Hervey et al., 2004) effects for commission errors on Conner's CPTs. Meta-analytic studies have consistently detected medium effects for child/adolescent ADHD on various measures of inhibition: total errors condition of the Matching Familiar Faces Test (Frazier et al., 2003), stop-signal reaction times (Frazier et al., 2003; Wilcutt et al., 2005), commission errors on traditional CPTs (Losier et al., 1996; Wilcutt et al., 2005), and the Stroop Color Word test (Pennington & Ozonoff, 1996). In a meta-analysis conducted by Pennington and Ozonoff (1996), a large effect was detected for a

motor inhibition composite (consisting of Go No-Go, Stopping, Anti-Saccade, Conflict Motor task, and NEPSY Inhibition).

It is plausible that ADHD partially accounts for reports of disinhibition in BP, as comparable levels of impairment tend to occur across both syndromes. Some studies have attempted to explicitly control for ADHD. Torralva et al. (2010) found that adults who had euthymic phase BP without ADHD performed similarly to controls on the Inhibitory Control measure from the Frontal Assessment Examination. In child/adolescent samples, Doyle et al. (2005) found that a BP group performed poorer on the Stroop Color Word test after controlling for ADHD, whereas Rucklidge (2006) did not. In two studies (Henin et al., 2007; Rucklidge, 2006), BP with comorbid ADHD groups did differ significantly from controls on this task. Rucklidge (2006) failed to detect any significant difference between a BP without ADHD group and controls in terms of commission errors on the Conners CPT. It is therefore plausible that ADHD symptom histories may only contribute to impaired performance on specific measures of inhibition

Given that meta-analytic research has consistently detected medium (Arts et al., 2009; Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006; Torres et al., 2007) effects for the Stroop Color Word test in adult euthymic phase BP, it is likely that lifetime ADHD comorbidity may contribute to, rather than account for, inhibition difficulties. The presence of lifetime ADHD may partially account for the small meta-analytic effect that has been detected for commission errors on CPTs in euthymic phase BP (Bora et al., 2009).

Memory and learning. Memory is a broad term that encompasses several distinct functions, each depending on different structures and circuits in the brain. In the most general terms, memory can be classified into two types, declarative and nondeclarative memory,

based on whether the retrieval of stored information is conscious or unconscious (Squire & Zola, 1996). Most research into ADHD and BP has focused on declarative memory, that is, the recall and/or recognition of past events (Squire & Zola, 1996). It is plausible that ADHD also contributes to declarative memory dysfunction in BP, as comparable levels of memory impairment have been observed in both syndromes. With regard to ADHD, the authors of a recent meta-analysis stated that “with the wide range and large number of memory tests used across adult ADHD studies, the consistency in finding effects is quite remarkable” (Hervey et al., 2004, p. 492). Indeed, the diagnostic criteria for ADHD as indexed by the DSM-IV-TR (2000) explicitly mention declarative memory problems, such as forgetfulness and absent-mindedness (“often loses things” and is “often forgetful”) (American Psychiatric Association, 2000, p. 92). It is unclear whether memory difficulties in ADHD are directly tied to memory processes, including problems with encoding, storage, or retrieval, or are an artefact of related cognitive processes such as attention or even inhibition (Hervey et al., 2004). Although impaired declarative verbal memory has been proposed as a trait marker for adult BP, researchers are unclear as to which processes actually predict this impairment (Bearden, Hoffman, & Cannon, 2001). Because studies of memory in adults with BP have generally failed to control for the potential cognitive impact of ADHD, it is possible that its undetected presence may have contributed to this confusion.

Short-term verbal memory or verbal working storage memory. Short-term or working storage memory can be defined by the ability to maintain selected information in seconds without being distracted in the process (Lezak, 2004). There is no time delay between stimulus presentation and rehearsal (Lezak, 2004). Word and number span tasks can be used to measure short-term verbal memory or verbal working storage memory (Lezak, 2004). According to the three-component model of human working memory, such measures activate a component of the model referred to as the phonological loop (Baddeley,

Gathercole, & Papagno, 1998). The phonological loop consists of two parts: a short-term phonological store with auditory memory traces that are subject to rapid decay and an articulatory rehearsal component that can revive the memory traces (Baddeley, Gathercole, & Papagno, 1998). It should be noted that word and number span tasks can also implicate the central executive component of the working memory system to varying degrees (Baddeley, Gathercole, & Papagno, 1998). Meta-analytic research has reported a moderate effect for adult ADHD using the immediate word recall condition of the California Verbal Learning Test (CVLT) (Hervey et al. 2004). Using the immediate recall condition of the Rey Auditory Verbal Learning Test (RAVLT), studies of children with ADHD have detected similar results (Felton, Wood, Brown, Campbell, & Harter, 1987; Loge, Station, & Beatty, 1990), though one study failed to detect a significant group difference (Cutting, Koth, Mahone, & Denckla, 2003). For the Digit Span Forwards task, meta-analytic studies have only detected small effects for this measure in adults (Boonstra et al., 2005) and children/adolescents (Martinussen et al., 2005) who have ADHD. It is possible that ADHD is less likely to have been associated with impairment on number sequencing tasks as performance is less dependent on the deployment of encoding strategies (Talley, 1986).

It is plausible that ADHD contributes to short-term verbal memory or verbal working storage memory deficits in BP, as comparable levels of impairment tend to occur across both syndromes. Several studies have attempted to investigate this issue. McClure et al. (2005) found that children/adolescents who had euthymic phase, depressed phase, mixed/manic phase BP without ADHD failed to differ significantly from controls on the immediate recall condition of the CVLT. In the same study, a BP with comorbid ADHD group did differ significantly from controls on this measure (McClure et al., 2005). On the Digit Span Forwards test, Torralva et al. (2010) noted that adults who had euthymic phase BP without lifetime ADHD failed to differ significantly from control groups. Such findings are

interesting because meta-analytic studies which failed to consider the effects of lifetime comorbid ADHD have consistently detected medium effects for adults with euthymic phase BP on the immediate recall conditions of various word learning paradigms (RAVLT, CVLT, or Visual Verbal Learning Test) (Bora et al., 2009; Robinson et al., 2006; Torres et al., 2007). Moreover, paralleling the ADHD literature, meta-analytic studies have only reported small effects for the Digit Span Forwards test among adults with euthymic phase BP (Arts et al., 2008; Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006). There appear to be no other controlled studies that consider word or digit span performance in children or adolescents with BP.

Verbal learning. Verbal learning ability is often used as a broad index of declarative memory. A commonly used paradigm involves the free recall of a list of related or unrelated words over five consecutive trials. Performance on such tests can benefit from the activation of the central executive component of the working memory system. Meta-analytic research has detected moderate (Schoechlin & Engel, 2005) and large (Hervey et al., 2004) effects for the verbal learning component of the CVLT in adult ADHD. Using word list paradigms, most studies of children with ADHD appear to have detected similar results. (Loge et al., 1990; Mealer, Morgan, & Luscomb, 1996; Øie, Sundet, & Rund, 1999).

It is plausible that comorbid lifetime ADHD may contribute to verbal learning impairment in BP, as comparable levels of impairment tend to occur across both syndromes. In a study which did not include a BP without ADHD group, children/adolescents who had manic BP with comorbid ADHD were impaired compared to controls on the CVLT verbal learning outcome measure (Henin et al., 2007). After controlling for the effects of ADHD, three studies failed to detect significant effects for verbal learning in child/adolescent BP samples (Doyle et al., 2005; McClure et al., 2005; Rucklidge, 2006). In the McClure et al. (2005) study, the presence of comorbid ADHD was associated with impairment. Nevertheless,

Rucklidge (2006) noted that adolescents who had euthymic phase BP with comorbid ADHD also performed similarly to controls. It is noteworthy that Rucklidge (2006) used the WRAML verbal learning condition as the psychometric properties of this test have been contested. In a study by Haut et al. (1992), the WRAML verbal learning condition was not found to clearly align with either a verbal or a visual memory factor. In opposition to most of this study's findings, Torralva et al. (2010) noted that adults who had euthymic phase BP without ADHD demonstrated significantly poorer verbal learning on the RAVLT compared to controls. It is significant that the number of mood episodes correlates with short-term memory impairment because in the Torralva et al. (2010) study, the average age of individuals in the BP without ADHD group was 41.3 years. Indeed, it is plausible that the natural increase in mood episodes over time may have largely accounted for this group's verbal learning impairment.

In contrast to most of the findings discussed above, meta-analytic studies which have failed to control for lifetime comorbid ADHD have detected strikingly different results. Using word list paradigms, including the RAVLT, CVLT, or Visual Verbal Learning Test, medium (Mann Wrobel et al., 2011), but generally large (Bora et al., 2009; Kurtz & Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007), meta-analytic effects have been detected for adults in euthymic phase BP. Large effects have been consistently reported for depressed (Kurtz & Gerraty, 2009) or mixed/manic phase BP (Kurtz & Gerraty, 2009).

Long-term verbal memory. Long-term memory is memory in which associations among items are stored. Long-term potentiation, which involves a physical change in the structure of neurons, has been proposed as the mechanism by which short-term memories move into long-term storage. Long-term verbal memory is typically measured with word list paradigms which require the recall of items after delays of at least 20 to 30 minutes (Kibby & Cohen, 2008). Meta-analytic research has detected a medium effect for the delayed recall

condition of the CVLT in adult ADHD (Hervey et al., 2004). Similar results have been found in studies which applied the delayed recall condition of the CVLT to children/adolescents with ADHD (Cutting et al., 2003; Loge et al., 1990; Øie et al., 1999).

It is plausible that comorbid lifetime ADHD may contribute to long-term verbal memory impairment in BP, as comparable levels of impairment also tend to occur across both syndromes. It is significant that impairment on the delayed recall condition of the CVLT was not reported in adult (Torralva et al., 2010) or adolescent (McClure et al., 2005) BP without lifetime comorbid ADHD groups. Such findings are of interest because meta-analytic studies have associated performance on the delayed recall conditions of word list paradigms with medium (Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006) or large effects in adults who have euthymic phase BP (Arts et al., 2008). Indeed, large effects for this measure have also been reported in a meta-analysis of adults who had mixed/manic BP. While ADHD may partially account for some of these meta-analytic results, it is also likely that they are partially a product of a natural increase in mood episodes over time.

Delayed verbal recognition memory. Delayed verbal recognition memory is most often assessed directly after the delayed recall condition of word list learning paradigms. Because it involves cued recall, performance is not considered to be particularly dependent on executive functioning (Torralva et al., 2010). For this reason, it has been suggested that individuals with ADHD are unlikely to be severely impaired on such tasks. It would appear that the performance of individuals with ADHD is largely dependent on the type of test that is used. For the delayed recognition component of the CVLT, a meta-analytic study of adult ADHD detected a large effect across two studies (Hervey et al., 2004). While one study detected significantly poorer performance on this measure in children/adolescents who had ADHD relative to controls (Cutting et al., 2003), a similar child/adolescent study did not (Øie

et al., 1999). Using the delayed recognition component of the RAVLT, studies of adults (Torralva et al., 2010) and children (Pollak, Kahana-Vax, & Hoofien, 2008) who had ADHD failed to detect any impairment relative to control groups. Similarly, Kibby and Cohen (2008) failed to detect an effect for delayed recognition memory in children who had ADHD relative to controls using the Children's Memory Scale Word Lists.

Given the variable performances of ADHD groups on measures of delayed verbal recognition memory, it is unclear whether this comorbidity is likely to contribute to impairment in BP. Two studies have attempted to investigate this issue. In the study by McClure et al. (2005), an adolescent BP with comorbid ADHD group performed significantly worse than controls on the CVLT whereas a BP without ADHD group did not. Conversely, Torralva et al. (2010) found that adults who had euthymic phase BP without lifetime comorbid ADHD were significantly impaired relative to both an ADHD group and controls on the delayed recognition component of the RAVLT. It is noteworthy that the BP without ADHD group was middle aged (average age of 41.3), as poor performance may have partially been a reflection of recurring mood episodes over time. Meta-analytic studies which have failed to control for ADHD have only detected small effects for delayed verbal recognition memory in adults with euthymic phase BP (Bora et al., 2009; Mann-Wrobel et al., 2011; Torres et al., 2007).

Short-term spatial memory or spatial working storage memory. According to the three-component model of human working memory identified above, short-term memory for spatial locations implicates a component of the model referred to as the visuospatial sketchpad. Specifically, the inner scribe sub-component of the visuospatial sketchpad is used in the temporary storage and manipulation of spatial information (Logie, 1995). Spatial working storage memory is also believed to be largely facilitated by attention-based rehearsal or covert shifts of spatial selective attention to memorized locations (Awh & Jonides, 2011;

Awh, Jonides, & Reuter-Lorenz, 1998). Unfortunately, virtually no studies have attempted to consider short-term spatial memory in adult ADHD. In two controlled studies that did include adult ADHD samples, there was a trend for significance on one measure (CANTAB Spatial Recognition Memory test) in one study (McLean et al., 2004) but no evidence of impairment on such measures in another study (Gropper & Tannock, 2009). It may have been difficult to detect group effects in the Gropper and Tannock (2009) study because it included a high IQ ADHD sample which may have been associated with a rather mild symptom presentation. These findings are somewhat surprising, given that meta-analytic research has detected a large effect for measures of short-term spatial memory in child/adolescent ADHD (Martinussen et al., 2005).

It is quite plausible that lifetime ADHD comorbidity may contribute to the variable findings of short-term spatial memory impairment in BP. Only two other studies have explicitly considered this issue (Dickstein et al., 2004; Rucklidge, 2006). Given that ADHD during childhood/adolescence is consistently associated with poor performance on the CANTAB Spatial Recognition Memory test in childhood ADHD relative to controls (Kempton et al., 1999; Rhodes, Coghill, & Matthews, 2005; Vance, Maruff, & Barnett, 2003), it is somewhat surprising that Dickstein et al. (2004) failed to detect an effect for this measure with child/adolescent controls and a euthymic phase BP sample, of whom 71% had ADHD comorbidity. Although Dickstein et al. (2004) failed to detect significant differences between BP with current comorbid ADHD ($n = 12$) and BP without current comorbid ADHD subgroups ($n = 10$), this result may not be that meaningful, as some participants in the latter group also had lifetime ADHD. In addition, the low sample sizes for these sub-groups may have made it difficult to detect significant effects. Nevertheless, Rucklidge (2006) failed to detect an effect for group on the WRAML Finger Windows test, an additional measure of short-term memory for spatial locations, in adolescents who were healthy or who had

euthymic phase BP without ADHD, ADHD, or BP with comorbid ADHD. It is important to note that the WRAML Finger Windows test has not been used in studies of child/adolescent BP that detected group effects for short-term spatial memory. Indeed, most of the paediatric BP studies have used the CANTAB Spatial Span and Spatial Recognition Memory tests as well as the Corsi Blocks task. It has been suggested that the Finger Windows subtest may be an unreliable measure of short-term spatial memory, as while Burton, Mittenberg, Gold, & Drabman (1999) found that it loaded on both attention/concentration and visual memory factors, Haut, Haut, & Franzen (1992) found that it was more highly correlated with measures of attention than with either verbal or nonverbal memory.

As demonstrated above, variable findings have been found for spatial memory performance in studies of adult BP that failed to control for lifetime ADHD comorbidity. Using the CANTAB Spatial Recognition Memory test, one study has detected impairment in euthymic phase BP relative to controls (Thompson et al., 2005) whereas another study has not (Braw et al., 2007). Similarly, while one further study found that adults who had depressed phase BP were impaired relative to controls on the SRM task (Rubinsztein, Tempest, Michael, Underwodd, & Sahakian, 2006), two additional studies did not (Roiser et al., 2009; Sweeney et al., 2000). Nevertheless, two additional studies of adult ADHD that failed to control for lifetime ADHD comorbidity did detect impairment among mixed/manic BP adults on this measure (Sweeney et al., 2000; Murphy et al., 1999). In contrast to the variable findings mentioned above, studies which used the CANTAB Spatial Span test but failed to control for lifetime ADHD comorbidity have consistently detected poorer performances in BP across euthymic phase (Thompson et al., 2005), depressed phase (Roiser et al., 2009), and mixed/manic phase (Sweeney et al., 2000; Badcock et al., 2005) mood states.

Short-term visual-object memory. According to the three-component model of human working memory, short-term visual-object memory also implicates the visuospatial sketchpad

component of this model. While the visual cache sub-component stores information about form and colour, the inner scribe sub-component rehearses such information and transfers it to the central executive (Logie, 1995). The nature of the short-term visual-object test appears to influence how individuals with ADHD perform. In two meta-analyses of adult ADHD, small to minimal effects were found for the WMS-R test of Visual Reproduction and the memory measures from the Rey Complex Figure Test (Hervey et al., 2004, Schoechlin & Engel, 2005). In children/adolescents, significant impairment has been detected for some tasks, including the CANTAB Delayed Matching to Sample test (Kempton et al., 1990; Rhodes et al., 2005; Vance et al., 2003) whereas meta-analytic studies have only detected small effects for other tests, including the Rey Complex Figure Test (Frazier et al., 2004).

In light of these variable findings, it is unclear whether the presence of lifetime comorbid ADHD is likely to partially account for the reports of short-term visual-object memory impairment in BP. Only two studies have explicitly investigated this issue. In a study that controlled for ADHD comorbidity, children/adolescents with euthymic phase hypomanic phase BP failed to differ significantly from controls in terms of accuracy on the CANTAB Pattern Recognition Memory test (Dickstein et al., 2004). Similarly, Rucklidge (2006) noted that BP with comorbid ADHD and BP-only groups both failed to differ significantly from controls on the WRAML Picture Memory subtest. In studies that failed to control for lifetime comorbid ADHD, findings of short-term visual-object memory impairment have been particularly variable. In two studies that also used the CANTAB Pattern Recognition Memory test, adult euthymic phase BP groups performed similarly to controls (Thompson et al., 2005; Braw et al., 2007). While significant impairment on the CANTAB Delayed Matching to Sample test has been detected in acutely depressed (Rubinsztein et al., 2006; Sweeney et al., 2000) and mixed/manic (Murphy et al., 1999; Sweeney et al., 2000) BP, the picture is unclear as some controlled studies which included depressed (Maalouf et al., 2010;

Roiser et al., 2009) or euthymic phase (Maalouf et al., 2010) BP failed to detect effects. Given that ADHD is typically associated with small effects on the immediate recall conditions of the Rey Complex Figure Test and the WMS-R Visual Reproduction test, its undetected lifetime presence is unlikely to fully account for the medium meta-analytic effects which have been detected for these tasks in adult euthymic phase BP (Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011). Given the large effects that have been reported for the DMS test in ADHD, it is plausible that this test, in particular, may differentiate a BP with comorbid ADHD group from a BP-only group.

Attention. Attention is basic for all cognitive processes. It refers to the means by which an organism becomes receptive to stimuli and begins to process incoming or attended-to excitation (Lezak, 2004). Attention is often divided into three categories: sustained attention (the ability to maintain a consistent behavioural response during continuous and repetitive activity), selective attention (the ability to maintain a behavioural or cognitive set in the face of distracting or competing stimuli), and divided attention (the ability to respond simultaneously to multiple tasks or multiple task demands). It is plausible that ADHD contributes to attentional difficulties in BP because, while comparable levels of significant attentional impairment (particularly difficulties with sustaining attention) occur across both syndromes, the effects of lifetime ADHD comorbidity on BP have rarely been considered. Together with inhibition, attention is the neuropsychological domain most closely identified with ADHD (Hervey et al., 2004). Indeed, for more than 25 years, conceptualisations of this disorder, or functionally equivalent disorders, have included attentional symptoms (DSM: 1980, 1987, 1994, 2000). Some investigators have suggested that deficits in sustaining attention may represent a trait deficit in BP (Najt et al., 2005). As Clark and Goodwin (2004) reveal, such difficulties are unrelated to residual mood symptomatology and medication status, and are present in individuals with good functional recovery. Moreover, difficulties

with sustaining attention are present early in the course of BP, but become more pronounced with repeated episodes (Clark & Goodwin, 2004). The present review is chiefly interested in the capacity to sustain attention, as indexed by performance on traditional continuous performance tests and measures that require concentration in conjunction with psychomotor skills.

Sustained attention. In the ADHD and BP literature, performance on continuous performance tests has often been measured through considering omission error (number of targets not responded to) and hit rates, response latencies and target sensitivity (ability to discriminate among stimuli). For adult ADHD, meta-analytic research has detected medium effects for omission error rates on continuous performance tests (Boonstra et al., 2005; Hervey et al., 2004) as well as medium (Hervey et al., 2004) or small (Boonstra et al., 2005) effects for tests that require psychomotor speed in addition to concentration such as the Trail Making Test-Part A. Similarly, for child/adolescent ADHD, meta-analytic research has detected medium effects for performance on continuous performance tests (Frazier et al., 2004; Losier, McGrath, & Klein, 1996; Willcutt et al., 2005) as well as small (Frazier et al., 2004) effects for tests that require psychomotor speed in addition to concentration.

It is quite plausible that lifetime ADHD comorbidity may contribute to the findings of attentional difficulties in BP. The few studies that have considered this issue have reported mixed results. Although Pavuluri et al. (2006) found that BP youth were impaired relative to controls on a sustained attention composite, impairment significantly increased with ADHD comorbidity. In a study that statistically controlled for ADHD comorbidity, a medium effect for omission errors was present on the Seidman Working Memory Auditory continuous performance test for children/adolescents who had BP relative to controls (Doyle et al., 2005). Although Rucklidge (2006) found that BP without ADHD and ADHD-only groups failed to differ significantly from controls in terms of omission errors on the Connor's

continuous performance test, a group that had BP with comorbid ADHD was impaired relative to controls on this measure. With regard to these latter findings, meta-analytic research suggests that it is more difficult to detect effects for ADHD on the Connor's continuous performance test and that this may be because it has a much higher signal probability (that is, many signals embedded among a few non-signal stimuli) than the more traditional continuous performance test (Hervey et al., 2004). Henin et al. (2007) failed to detect a statistically significant difference between a BP with comorbid ADHD group and controls while using the Seidman Working Memory Auditory continuous performance test.

Given that meta-analytic research has consistently detected medium (Arts et al., 2009; Kurtz & Gerraty, 2009) or large (Bora et al., 2009; Torres et al., 2007) effects for CPT outcome measures in adult euthymic phase BP, it is possible that lifetime ADHD comorbidity may contribute to, rather than account, for attentional difficulties. The severity of mood symptomatology may also amplify impairment as a meta-analytic study associated mixed/manic adult BP with a large effect size relative to controls. Interestingly, other meta-analytic research which has failed to control for lifetime ADHD comorbidity has also consistently detected moderate (Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006; Torres et al., 2007) effects for euthymic phase adult BP and large effects for mixed/manic or depressed phase adult BP on tests that require psychomotor speed in addition to concentration. Therefore, once again, the presence of lifetime ADHD comorbidity may contribute to rather than account for impairment on such measures.

Psychomotor speed and processing speed.

Psychomotor speed is the amount of time that it takes a person to process a signal, prepare a response and execute that response. In ADHD, performances on measures of psychomotor speed appear to vary considerably depending on the nature of the test. Tasks that involve low

information processing loads have been associated with non-significant (reaction times on the Conners CPT, the three second delay condition of the Delayed Oculomotor Response Task, and the Simple task from the 3RT test) or small (traditional CPT reaction times) meta-analytic effects in adult ADHD (Hervey et al., 2004). In the absence of meta-analytic research, attention is given to specific child/adolescent studies which have controlled for developmental coordination disorder, and have included tests that require minimal hand-eye coordination. In three controlled studies of ADHD that used the Finger Tapping Test, no significant group differences were detected (Meyer & Sagvolden, 2006; Seidman, Biederman, Faraone, Weber, & Ouellette (1997).

In studies of adult ADHD, tasks which involve a degree of verbally mediated processing (Stroop Color and Word conditions) have been associated with small (Hervey et al., 2004) or medium (Boonstra et al., 2005) effects. A medium meta-analytic effect has also been detected for adult ADHD using the Coding test (Hervey et al., 2004). Consistent with the adult literature, it is those measures of psychomotor speed which implicate medium to high information loads that are associated with the highest levels of impairment in child/adolescent ADHD. The Processing Speed Index and its component measures have been associated with large meta-analytic effects for child/adolescent ADHD (Frazier et al., 2004).

It is unlikely that ADHD contributes to simple psychomotor speed difficulties in BP as neither syndrome tends to be associated with such impairment in this cognitive domain. Like ADHD, individuals with BP tend to perform relatively normally on measures of psychomotor speed which involve low information loads. Two child/adolescent studies have considered the relative contribution of ADHD. In one study, a euthymic phase BP with comorbid ADHD group performed similarly to a euthymic phase BP-only group and controls on the CANTAB Motor Screening test (Dickstein et al., 2004). In addition, Pavuluri et al. (2006) found that children or adolescents who had euthymic phase BP with or without comorbid ADHD did not

differ from controls on the finger tapping speed test from the Cogtest battery. In studies that failed to control for ADHD, Braw et al. (2007) noted that euthymic phase adults performed similarly to controls on the CANTAB Motor Screening test and Sweeney et al. (2000) found that adults who had mixed/manic BP or depressed BP failed to differ significantly from controls on two additional CANTAB subtests that measure psychomotor speed: Five Stage Reaction Time test, and the Big Circle/Little Circle test.

While BP is also more likely to be associated with impaired performance on measures of psychomotor speed that include medium to high levels of information processing, this may be due in part to the presence of lifetime ADHD. Two studies have considered the relative contribution of ADHD (Doyle et al., 2005; Rucklidge, 2006). In one child/adolescent study, a BP without ADHD group failed to differ significantly from controls on a processing speed composite and its two component tasks (Processing Speed Index from the WISC/WAIS-III), the Stroop Color or Word conditions, or on any of the five Rapid Automatized Naming (RAN) outcome measures (Numbers, Letters, Colors, Objects, Color/Number/Letter) (Rucklidge, 2006). Conversely, the BP with comorbid ADHD group performed significantly poorer than the BP without comorbid ADHD group on the Stroop Word condition, and from controls on the Processing Speed Index, its Coding component test, the RAN Colors test, and the Stroop Word test (Rucklidge, 2006). After controlling for ADHD, Doyle et al. (2005) found that BP was associated with poor performances relative to controls on the Coding and Stroop Color tests, but similar performances on the Symbol Search or Stroop Word conditions. Henin et al. (2007) failed to detect any significant differences between BP with comorbid ADHD groups and controls on the following measures of processing speed: Coding; Symbol Search; Stroop Word; Stroop Color. In light of these results, it is quite plausible that the presence of ADHD partially explains findings of moderate (Bora et al., 2009; Kurtz & Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007) to large (Arts et al.,

2008) meta-analytic effects in adults who have euthymic phase BP on the Digit Symbol Substitution Test. In adults who have euthymic phase BP, medium meta-analytic effects have also been detected for the Stroop Word and Stroop Color conditions (Mann-Wrobel et al., 2011).

Age and Developmental Aspects of Neuropsychological Functioning

Neuropsychological studies need to carefully consider the effects of age and the developmental aspects of neuropsychological functioning. As Lezak (2004) summarises, the development of many cognitive functions is maturational and is relatively independent of social learning.

A great deal of research demonstrates that among normal individuals, there are systematic, age-related improvements in executive functioning during childhood and into adolescence (for review, see Zelazo & Muller, 2002). Given that executive functioning declines during aging (for a review see Mayr, Spieler, & Kliegl, 2001), its development is believed to follow an inverted U-shaped curve (Dempster, 1992). In ADHD, children and adults both demonstrate remarkably similar levels of executive dysfunction (see review above and Hervey et al., 2004). Nevertheless, given that some executive functioning deficits in ADHD are slightly more pronounced in children, including cognitive flexibility as indexed by the Wisconsin Card Sorting Test, it is plausible that impairment in this domain may partly reflect a maturational lag in brain development (Hervey et al., 2004). Nevertheless, this seems unlikely as other tests are highly associated with executive functioning: TMT-B, and the COWAT (Hervey et al., 2004). Hence, it is plausible that tests like the WCST measure different skills in children as compared with adults or are simply too easy for adults (Hervey et al., 2004). Neurobiological research supports the notion that executive dysfunction is relatively stable in ADHD across the lifespan. In children with ADHD, performance on

inhibition tasks correlated only with those anatomical measures of fronto-striatal circuitry observed to be abnormal in ADHD (i.e., the prefrontal cortex, caudate, and globus pallidus) (Casey et al., 1997; Semrud-Clikeman et al., 2000). Similarly functional imaging studies of adults, provide evidence that the anterior cingulate (Bush et al., 1999), prefrontal cortex (Schweitzer et al., 2000) and cerebellum (Valera, Faraone, Biederman, Poldrack, & Seidman, 2005) are compromised relative to controls. Whereas children and young adults with BP appear to demonstrate similar levels of executive dysfunction (see Executive functioning subsection above), older adults may be particularly compromised. With regard to older samples, Friedman, Culver & Ferrell (1977) reported that euthymic phase BP individuals aged ≥ 59 yr performed much poorer than younger individuals with BP on the Halstead–Reitan index. Neuroimaging studies suggest that the prefrontal cortex, which as alluded to above, is associated with executive functioning is similarly affected in children and adults with BP (see Keener & Philips, 2007 for a review).

In general, behavioral evidence demonstrates that in normal individuals, general declarative mnemonic abilities develop from childhood, through adolescence, and into young adulthood (Schneider and Pressley, 1997). With this being said, forms of memory requiring less conscious control develop earlier than forms of memory that require considerable degrees of strategy use (Gathercole, 1998). Older adults show poorer performance than younger adults on explicit memory tasks, with the difference in performance being largest in free recall, (Craig and McDowd, 1987). Also, both younger children and older adults have been shown to encounter difficulties in the ability to specify contextual information surrounding memory traces (source monitoring) relative to younger adults (Johnson, Hashtroudi, & Lindsay, 1993). There is also differential reliance on familiarity and recollection retrieval processes across the lifespan as the development of recollection extends into adolescence, whereas familiarity matures earlier during childhood (Brainerd and Reyna, 2004; Ghetti & Angelini,

2008). Older adults have been found to rely more on familiarity processes during retrieval as they face difficulties in recollecting details of memory episodes (Healy, Light, & Chung, 2005). Finally, there are believed to be changes in the organisation of memory representations as children having good access to the lower-level details of episodic instances and then gradually build up higher level concepts whereas older adults retain access to higher conceptual levels but progressively lose access to the lower levels (Shinga et al., 2010).

As demonstrated in the Memory and learning sub-section above, there is a great deal of evidence suggesting that verbal and nonverbal memory impairments remain relatively stable across child and adult ADHD and BP samples. Research with neurosurgical patients and neuroimaging studies demonstrate that verbal and nonverbal memory tests implicate a number of brain regions, particularly the temporal lobes (Monk et al., 2002; Owen, Sahakian, Semple, Polkey, & Robbins Owen, 1995; Picchioni et al., 2007) and the anterior cingulate cortex (Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002; Picchioni et al., 2007). In children and adults with ADHD, neurobiological studies have revealed that such brain regions are often compromised (Castellanos et al., 2002; Sowell et al., 2003; Bush et al., 1999; Rubia et al., 1999; Seidman et al., 2006; Tamm, Menon, Ringel, & Reiss, 2004; Tian et al., 2006). Similarly, neurobiological studies of BP have also detected impairment in these brain regions among children (Dickstein et al., 2005) and adults with BP (Strakowski, et al., 2005).

For the purposes of this thesis, the proceeding review will focus on research regarding sustained attention or vigilance abilities throughout the lifespan. As is the case for executive functioning, sustained attention appears to be characterised by a U-shaped pattern of performance across the lifespan. Specifically, a great deal of evidence suggests that this skill improves markedly during childhood (Day, 1978; Kaye & Ruskin, 1990; Miller, 1973; Thompson & Mas-saro, 1989; Vurpillot, 1968) and deteriorates in later life (Plude, 1990;

Plude & Doussard-Roosevelt, 1989; Rabbitt, 1965). Nonetheless, certain component skills appear to be differentially affected by age. Whilst feature binding (or movement of attention to a single item) shows evidence of early maturation with little deterioration over time, the voluntary movement of spatial attention in particular follows a pattern of late maturation and significant decline in late adulthood (Trick & Enns, 1998). As the Attention sub-section above indicates as well as a review by Seidman (2006), difficulties with sustaining attention remain relatively stable across the lifespan in ADHD. A few neuroimaging studies have considered the performance of individuals with ADHD during tests of sustained attention. Results tend to implicate similar regions of brain impairment in children and adults with ADHD. In a study of children, ADHD was associated with reduced functional connectivity relative to controls between the inferior frontal cortex, basal ganglia, and parietal lobes, and between the cerebellum, parietal and striatal brain regions during a sustained attention task (Rubia, Halari, Cubillo, Mohammad, & Taylor, 2009). In a study by Cubillo, Halari, Smith, Taylor, & Rubia (2011), adults who had ADHD showed dysfunctions in lateral fronto-striatal-parietal regions relative to controls during a CPT. With regard to BP, regional activation decrements in the dorsolateral prefrontal cortex have been shown to accompany sustained attention decrements in BP adults (Fleck et al., 2012). As mentioned above, neuroimaging studies of children with BP have identified impairment in this brain region (Keener & Philips, 2007)

For the purposes of the present study, the following review considers basic psychomotor speed across the lifespan. Whilst the results of a meta-analytic study demonstrate that basic psychomotor speed improves from childhood to young adulthood (Thomas & French, 1987), other studies indicate that it then decreases in old age (Adler, Hentz, Joyce, Beach, & Caviness, 2002; Smith et al., 1999). Indeed, a recent study confirmed this overall pattern using four different age bands ranging from 7 to 79 years (Leversen, Haga, & Sigmundsson,

2012). As discussed in the Psychomotor speed and processing speed sub-section, studies of children and adolescents (Meyer & Sagvolden, 2006; Seidman, Biederman, Faraone, Weber, & Ouellette, 1997) as well as meta-analytic research of adults (Hervey et al., 2004) have generally failed to detect effects on measures of simple psychomotor speed for ADHD. The same pattern has held for children/adolescents (Dickstein et al., 2004; Pavuluri et al., 2006) and adults (Braw et al., 2007; Sweeney et al., 2000) with BP. Neuroimaging research indicates that simple psychomotor speed tests primarily implicate brain regions such as the premotor cortex (Johansen-Berg et al., 2002) and the primary motor cortex (Liuzzi et al., 2010) which are not typically associated with the neuropathology of ADHD (Valera, E. M., Faraone, S. V., Murray, K. E., & Seidman, 2007), and BP (Strakowski et al., 2005; Keener & Philips, 2007) during either childhood or adulthood.

Limitations of Past Research

The validity of research that has detected neuropsychological impairment in BP populations (regardless of whether lifetime ADHD has been controlled for or not) is often questionable with many studies failing to control for the potential cognitive effects of non-clinical variables, including IQ, and clinical variables such as the presence of past psychosis, past child abuse, nicotine/caffeine use, and medication. Given that IQ is known to impact negatively on verbal declarative memory (Bora et al., 2007; Ferrier et al., 1999), nonverbal memory (Lezak, 2004), and executive functioning (Denckla, 1996), it is unfortunate that some neuropsychological studies of BP that controlled for lifetime ADHD, failed to covary IQ (McClure et al., 2005; Dickstein et al., 2004). Similarly, it is concerning that many of the studies of BP which have failed to control for lifetime ADHD (some of these studies have been included in meta-analytic studies), also neglected to covary IQ (Kolur, Reddy, John, Kandavel, & Jain, 2006; Varga, Magnusson, Flekkoy, Ronneberg, & Opjordsmoen, 2006; Bora et al., 2007; Dittman et al., 2007). Given the high rates of child abuse within BP

populations (Garno et al., 2005; Hyun et al., 2000; Leverich et al., 2002) and its association with verbal declarative memory problems, it is also notable that the five other studies of BP that controlled for the effects of lifetime ADHD (Rucklidge, 2006; McClure et al., 2005; Pavulri et al., 2006; Mattis et al., 2011; Dickstein et al., 2004) failed to covary child abuse. Moreover, not one of the BP studies that failed to control for lifetime ADHD considered the impact that child abuse may have had on RAVLT performance (Bora et al., 2007; Ferrier, Stanton, Kelly, & Scott, 1999; Goswami et al., 2006; Krabbendam et al., 2000; Schouws, Zoeterman, Comijs, Stek, & Beekman, 2007; Thompson et al., 2005; Varga et al., 2006).

It is also unhelpful that measures of lifetime psychotic phenomena have not been included in many neuropsychological studies of BP as this too has been shown to interfere with verbal declarative memory (Bora et al., 2007) and executive functioning (Bora et al., 2010). Indeed, none of the studies that controlled for lifetime ADHD included such a measure (Rucklidge, 2006; McClure et al., 2005; Pavulri et al., 2006; Mattis et al., 2011). This was also the case for most of the studies that applied the RAVLT to BP populations but failed to control for lifetime ADHD (Ferrier et al., 1999; Goswami et al., 2006; Thompson et al., 2005; Varga et al., 2006). Indeed, most of the other studies that applied executive functioning measures (including the TMT-B, COWAT, DSB, or SWM tests) to BP populations failed to control for the possible impact of lifetime psychotic features (Barrett et al., 2008, Braw et al., 2007; Cavanagh, Van Beck, Muir, & Blackwood, (2002); Clark et al., 2002; Dittman et al., 2007; Ferrier et al., 1999; Goswami et al., 2006; Martinez-Aran et al., 2007; Nehra, Chakrabarti, Pradhan, & Khehra, 2006; Pirkola et al., 2005; Rosier et al., 2009; Smith, Muir, & Blackwood, 2006; Stoddart, Craddock, & Jones., 2007; Sweeney et al., 2000; Thompson et al., 2005; Thompson et al., 2007; Van Gorp, Altshuler, Theberge, Wilkins, & Dickson, 1998; Varga et al., 2006; Zalla et al., 2004; Zubieta, Huguelet, O'Neil & Giordani, 2001).

It is also notable that many studies have failed to control for the potential negative effects of the medications typically used to treat BP as such medications have been shown to interfere with cognitive functioning, particularly verbal declarative memory (Amado-Boccaro et al., 1995; Balanza-Martinez et al., 2010; Honig, Arts, Ponds, & Riedel, 1999; Patchet & Wisniewski, 2003). Whereas one of the studies that controlled for lifetime ADHD failed to covary the effects of medications (Rucklidge, 2006), this was the case for a number of studies that used the RAVLT but neglected to control for lifetime ADHD (Ferrier et al., 1999; Goswami et al., 2006; Krabbendam et al., 2000; Schouws et al., 2007; Thompson et al., 2005; Varga et al., 2006). It is also unfortunate that many neuropsychological studies of BP have failed to control for the effects of mood symptoms as these have the potential to impact on a number of cognitive skills: declarative verbal memory (Kurtz & Gerraty, 2009), nonverbal memory (Braw et al., 2007; Roiser et al., 2009; Rubinsztein et al., 2006; Sweeney et al., 2000), and sustained attention (Kurtz & Gerraty, 2009). Indeed, two studies that controlled for the effects of lifetime ADHD failed to consider the impact of residual mood symptoms (Rucklidge, 2006; Dickstein et al., 2004) on these domains. Of those studies that failed to control for lifetime ADHD, some have also neglected to consider the impact of such symptoms on RAVLT performance (Krabbendam et al., 2000; Schouws et al., 2007; Varga et al., 2006).

Whereas nicotine consumption (using the Identical Pairs CPT) (Barr et al., 2008) has been associated with sustained attention and executive functioning performance, caffeine consumption (using the Scanning Visual Vigilance test) (Lieberman, Tharion, Shukitt-Hale, Speckman, & Tulley, 2002) has also been shown to impact on sustained attention. In light of such findings, it is problematic that none of the studies that controlled for the effects of lifetime ADHD considered the impact of nicotine or caffeine consumption on such cognitive skills, (Rucklidge, 2006; Pavulri et al., 2006; Mattis et al., 2006). Similarly, of the studies that

failed to control for lifetime ADHD but employed measures of sustained attention (TMT-A or RVIP) or executive functioning (TMT-B, COWAT, DSB, or SWM tests) identical to those used in the present investigation (see below), there was not one that considered the effects of nicotine or caffeine consumption (Altshuler et al., 2004; Bora et al., 2007; Braw et al., 2007; Clark et al., 2001; Clark et al., 2002; Clark et al., 2005; Dittman et al., 2007; Ferrier et al., 1999; Goswami et al., 2006; Krabbendam et al., 2000; Maalouf et al., 2010; Martinez-Aran et al., 2004; Martinez-Aran et al., 2007; Nehra et al., 2006; Schouws et al., 2007; Smith et al., 2006; Stoddart et al., 2007; Thompson et al., 2005; Torrent, Martinez-Aran, & Daban, 2006; 2006; Van Gorp et al., 1998; Varga et al., 2006; Zalla et al., 2004; Badcock et al., 2008; Pirkola et al., 2005; Rosier et al., 2009; Sweeney et al., 2000; Thompson et al., 2007; Zubieta et al., 2001).

It is also notable that learning disorders have the potential to impact on executive functioning (Seidman, 2006). Unfortunately, none of the four studies that controlled for the effects of lifetime ADHD on executive functioning covaried the effects of learning disorders (Rucklidge, 2006; Dickstein et al., 2004; Pavuluri et al., 2006; Mattis et al., 2011). Of the studies of BP that failed to control for ADHD, the vast majority failed to control for the effects of learning disorder on the TMT-B, COWAT, DSB, or SWM test (Altshuler et al., 2004; Bora et al., 2007; Braw et al., 2007; Clark et al., 2002; Dittman et al., 2007; Krabbendam et al., 2000; Martinez-Aran et al., 2007; Nehra et al., 2006; Rosier et al., 2009; Schouws et al., 2007; Smith et al., 2006; Stoddart et al., 2007; ; Sweeney et al., 2000; Thompson et al., 2005; Thompson et al., 2007; Van Gorp et al., 1998; Varga et al., 2006; Zalla et al., 2004; Zubieta et al., 2001).

It is also problematic that many of the aforementioned studies have applied stringent exclusion criteria to the groups in question. This reduces the generalisability of the findings as current or lifetime Axis I comorbidities are likely to be absent or detected at rates much

lower those reported for the general population. Also, the prevalence of type I error is likely to increase as group effects on cognitive measures are more likely when control groups demonstrate few psychiatric features. Indeed, there is evidence that in healthy adults, verbal declarative memory and nonverbal memory can be adversely affected by the presence of comorbid disorders, including substance dependence (Levy, Monzani, Stephansky, & Weiss, 2008) or anxiety disorders (Hsiao et al., 2009). Similarly, the presence of anxiety disorders has also been shown to compromise sustained attention (Hsiao et al., 2009). Indeed, many neuropsychological studies of BP have applied stringent inclusion criteria to control groups. This has been the case for some studies of BP that controlled for lifetime ADHD (McClure et al., 2005; Dickstein et al., 2004) and almost every study of BP that failed to control for lifetime ADHD (Ferrier, Stanton, Kelly, & Scott, 1999; Goswami et al., 2006; Kaya et al., 2007; Krabbendam et al., 2000; Schouws, Zoeterman, Comijs, Stek, & Beekman, 2007; Thompson et al., 2005; Bora et al., 2007; Varga et al., 2006; Braw et al., 2007; Maalouf et al., 2010; Murphy et al., 1999; Rubinsztein et al., 2006; Badcock et al., 2005; Sweeney et al., 2000; Roiser et al., 2009; Clark et al., 2001; Clark et al., 2002; Clark et al., 2005; Altshuler et al., 2004; Dittman et al., 2007; Kolur et al., 2006; Martinez-Aran et al., 2004; Martinez-Aran et al., 2007; Nehra et al., 2006; Stoddart et al., 2007; Torrent et al., 2006; Van Gorp et al., 1998; Zalla et al., 2004; Thompson et al., 2007; Zubieta et al., 2001).

It is unfortunate that only one other neuropsychological study explicitly compared BP with and without lifetime ADHD groups to ADHD-only groups and control groups (Rucklidge, 2006). Such a comparison among four groups is most effective at clarifying whether ADHD contributes to neuropsychological impairment in BP. Pavuluri et al. (2006) and Dickstein et al. (2004) fail to compare each BP subgroup to ADHD-only or control groups. Whereas McClure et al. (2005) compare the two BP subgroups to a control group, Mattis et al. (2006) compares the two BP subgroups to an ADHD-only group.

A further limitation of previous research is that there are no neuropsychological studies of adults which have compared BP with and without lifetime ADHD groups. Rather, the five studies which have compared BP with and without lifetime ADHD groups have only included child/adolescent samples (Dickstein et al., 2004; Mattis et al., 2006; McClure et al., 2005; Pavuluri et al., 2006; Rucklidge, 2006). This is concerning given that cognitive problems may contribute to the high rates of interpersonal violence, suicide attempts, legal problems, and poor social functioning outcomes, in adults who have BP with a history of ADHD (Ryden et al., 2009; Nierenberg et al., 2005; Sentissi et al., 2008).

Variables that may Impact on Neuropsychological Functioning

Unfortunately, many studies of BP and ADHD have failed to adequately consider whether group differences on neuropsychological measures are influenced by covariates. Indeed, there is evidence that such studies should consider the cognitive effects of substance use, learning disorder, mood symptomatology, the presence of past child abuse or past psychotic features, medication, clinical subtype, cigarette and caffeine use, bipolar-specific variables (illness duration, age of onset, number of manic or depressive episodes, number of hospitalisations), and demographic (age, sex, ethnicity) variables.

Clinical characteristics that may impact on cognitive functioning.

Substance use disorders. Substance use comorbidity is particularly common in BP as well as in ADHD. Most neuropsychological studies have tended to focus on the cognitive effects of either alcohol use disorders, or substance use disorders in general (e.g. alcohol, cannabis, opiates, etc). The cognitive effects of alcohol use disorders requires particular attention as a wide body of research conducted with healthy humans and animals suggests that alcohol can generate significant cognitive impairment, especially in the domains of

verbal memory and executive functioning (Medina, Shear & Schafer, 2006; Sullivan & Pfefferbaum, 2005; Verdejo-Garcia, Bechara, Recknor & Perez-Garcia, 2006).

It is unlikely that the presence of alcohol use disorders or other substance use disorders can account for the full gamut of neuropsychological impairment observed in BP. Three studies have identified a broad range of neuropsychological deficits in BP samples after excluding participants with a history of alcohol/substance abuse (Cavanagh et al., 2002; Sanchez-Moreno et al., 2009; Savitz, van der Merwe, Stein, Solms, & Ramesar, 2008), or alcohol/substance dependence (Cavanagh et al., 2002; Sanchez-Moreno et al., 2009).

Nevertheless, a study which included small sample sizes found that verbal and visual memory difficulties in BP were only associated with current alcohol dependence (Levy et al., 2008). In another study, cognitive inflexibility, and difficulties with short-term and delayed verbal memory were only detected in BP individuals with past alcohol dependence (Van Gorp et al., 1998). It is still unclear whether comorbid alcohol or substance use disorders contribute to worse neuropsychological outcomes in BP.

A great deal of research suggests that the significant relation between ADHD and neuropsychological impairment (particularly executive dysfunction) cannot be explained by the presence of comorbid alcohol/substance use disorders, (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Nigg, 2001; Nigg Blaskey, Huang-Pollock, & Rappley, 2002; Nigg, Hinshaw, Carte, & Treuting, 1998; Rucklidge & Tannock, 2002; Willcutt et al 2001, Willcutt, Pennington, Chhabildas, Olson, & Hulslander, 2005). Nevertheless, it is unclear as to whether comorbid alcohol/substance use disorders worsen neuropsychological profiles in ADHD.

Learning disorder. Learning disorders by definition are neurocognitive disorders, and hence they have the potential to significantly compromise cognitive functioning. At present,

it is unclear whether or not learning disorders are prevalent in BP. While academic difficulties are often detected in BP, particularly difficulties with mathematics (Lagace, Kutcher, & Robertson, 2003), such problems are usually attributed to adjustment problems, the effects of multiple hospitalizations, and difficulties with peers, rather than to a learning disorder per se (Salzman & Salzman, 1989; Weiner & Weine, 1996). Future studies need to establish whether the presence of learning disorder partially accounts for findings of neurocognitive impairment in BP.

As mentioned previously, learning disorders are frequently comorbid with ADHD. In the review by Seidman (2006), executive functioning deficits were consistently shown to be exacerbated by co-morbidity with learning disorders, including reading disorder. Other studies have associated comorbid reading disorder with greater impairment on measures of attention (August & Garfinkel, 1990; Tarnowski, Prinz, & Nay, 1986), and memory functions (verbal and visual) (August and Garfinkel, 1990; Katarina, Hall, Wong, & Keys, 1992). Nonetheless, a study by Halperin, Gittelman, Klein & Rudel (1984) did not find greater impairment among a group with ADHD and comorbid reading disorder on measures of memory, attention, and visual-motor functioning. Due to a dearth of published studies, it is unclear whether other learning disorders such as mathematics disorder contribute to cognitive impairment in individuals with ADHD (Seidman, 2006).

Anxiety. It is noteworthy that neuropsychological examinations can be a source of anxiety (Bennett-levy, Klein-boonschate, Batchelor, McCarter, & Walton 1994), as high levels of state anxiety can enhance distractibility (Eysenck, 1991), and contribute to processing speed difficulties as well as memory failure (Buckelew & Hannay, 1986; King, Hannay, Masek, & Burns, 1978; Sarason, Sarason, Keefe, Hayes, & Shearin, 1986). It is therefore desirable if instruments such as the State Anxiety Inventory are administered at the beginning of a neuropsychological test battery. Neuropsychological studies should also

consider whether anxiety disorders are present. Indeed, primary diagnoses of anxiety disorder are associated with poor neuropsychological outcomes, particularly in the executive function, attention, and verbal memory domains (Asmundson, Stein, Larsen, & Walker, 1994; De Geus, Denys, Sitskoorn, & Westernberg, 2007; Ludewig, Paulus, Ludewig, & Vollenweider, 2003; Mantella et al., 2007; McNally, 2006; Nielen & Den Boer, 2003; Toren et al., 2000).

As demonstrated in an earlier section (refer to Comorbidity and its Clinical Impact on Bipolar Disorder), BP is frequently comorbid with anxiety disorder. Only one study appears to have explicitly considered whether comorbid anxiety disorder impacts on cognitive functioning in BP. In a recent study by Hsiao et al. (2009), BP-II patients with comorbid anxiety disorders showed poorer neuropsychological outcomes (short-term verbal and visual memory, long-term verbal and visual memory, sustained attention, and working memory) than those in BP-II-only and control groups. Across these tests, the BP-II-only and control groups performed similarly. The contribution of anxiety disorders to cognitive functioning in BP-I requires attention.

Comorbid anxiety disorders are also common in ADHD. Some studies of children with ADHD and comorbid anxiety disorder have detected poorer working memory outcomes (Brocki & Bohlin, 2006; Tannock, Ickowicz, & Schachar, 1995). Indeed, recent reviews underline the controversial role of anxiety disorder comorbidity in worsening working memory deficits in ADHD children (Brocki & Bohlin, 2006; Schatz & Rostain, 2006). Nevertheless, most other forms of cognitive impairment do not appear to be influenced by anxiety disorder comorbidity in ADHD (Oosterlaan & Sergeant, 1998; Sarkis, Sarkis, Marshall, & Archer, 2005).

The severity of mood symptomatology. The presence of severe mania and/or depression symptoms can contribute to neuropsychological impairment. With regard to BP,

the previous review demonstrated that larger meta-analytic effects were detected on measures of verbal fluency and sustained attention when mixed/manic, or depressed symptoms were present (Kurtz & Gerraty, 2009). Similarly, larger effects were more likely to be demonstrated on measures of short-term visual memory (Murphy et al., 1999; Sweeney et al., 2000) and long-term verbal memory (Kurtz & Gerraty, 2009) among mixed/manic samples. It would seem that more research is required in order to ascertain whether mood severity in BP can significantly impact on cognitive functions such as verbal working memory, inhibition, processing speed, and delayed verbal recognition memory.

In ADHD, the presence of comorbid depression does not appear to significantly worsen cognitive performance. In studies of child/adolescent ADHD, the presence of depression (Fischer, Barkley, Smalish, & Fletcher, 2005) and internalising disorders more generally has not been related to neuropsychological functioning (Trani et al., 2011).

Psychotic features. Given that psychotic disorders (particularly schizophrenia) are often associated with high levels of cognitive impairment relative to other DSM-IV-TR, it is important that neuropsychological studies consider whether psychotic features have ever been present. According to Keck et al. (2003), approximately 50% of BP individuals experience psychotic features at some point in their illness. It would seem that a history of psychosis predisposes BP individuals to experiencing more severe neurocognitive impairment, especially in the domain of executive functioning. In a recent meta-analysis, BP individuals with a history of psychosis performed significantly worse than BP individuals who had never had psychosis across measures of executive functioning (planning and reasoning, working memory, processing speed, semantic fluency), and verbal memory, but not on measures of visual memory or sustained attention (Bora, Yücel, & Pantelis, 2010). A recent study by Allen et al. (2010) found that psychosis in BP may specifically impair the executive control component of working memory. Such findings are in parallel with results of some

neuroimaging and electrophysiological studies suggesting that there are more severe brain structural and functional abnormalities in BP individuals with a history of psychosis (Bora, Yücel, Fornito, Berk, & Pantelis, 2008; Olincy & Martin, 2005; Pearlson et al., 1995; Sanchez-Morla et al., 2008; Strasser et al., 2005).

Research has failed to consider whether psychotic symptoms contribute to worse neuropsychological outcomes in ADHD. Most neuropsychological studies have only compared ADHD with youth onset psychotic disorder. It is plausible that a history of psychotic symptoms contributes to worse neuropsychological outcomes in ADHD as youth psychotic disorder is more likely to be associated with greater difficulties in certain cognitive areas: divided attention (Karatekin, White, & Bingham, 2008), and visual memory (Øie et al., 1999).

Clinical subtype. When conducting neuropsychological assessments with BP samples, it is important to note that the cognitive profiles of BPI and BP II will often vary in subtle ways. Most studies have reported that it is individuals with BPI and not BP II who experience difficulties with verbal memory and learning compared to controls (Hsiao et al., 2009; Savitz et al., 2008; Simonsen et al., 2008). There is also evidence that BP II rather than BPI is more likely to be associated with poorer spatial working memory (Summers, Papadopoulou, Bruno, Cipolotti, & Ron, 2006) and slower psychomotor speed (Harkavy-Friedman et al., 2006) relative to controls. It would seem that BPI and BP II groups are generally similarly impaired relative to controls with respect to processing speed (Ha et al., 2008; Harkavy-Friedman et al., 2006), attention (Hsiao et al., 2009; Torrent et al., 2006), and verbal working memory (Harkavy-Friedman et al., 2006; Torrent et al., 2006; Simonsen et al., 2008). For other cognitive functions, results are inconsistent with respect to whether the BPI and BP II groups differ significantly from controls and each other.

Most of the investigations that have examined the neuropsychological profiles of ADHD subtypes have only compared the Combined and Inattentive subtypes. Moreover, such studies have tended to only consider executive functioning. In the Wilcutt et al. (2005) meta-analysis, few consistent differences were detected between the combined and inattentive types on any executive function measure. Only a few studies have considered the hyperactive-impulsive subtype. In general, they are associated with minimal executive impairment (Bedard et al 2003; Chhabildas, Pennington, & Willcutt, 2001; Schmitz et al., 2002).

Childhood abuse. It can be helpful if neuropsychological studies consider the potential cognitive effects of child abuse. Childhood abuse appears to impact negatively on neuropsychological functioning; especially in the areas of verbal memory (Bremner et al., 1995; Bremner, Vermetten, Afzal & Vythilingam, 2004) and inhibition (Navalta, Polcari, Webster, Boghossian & Teicher, 2006). Indeed, neuroimaging studies have correlated childhood abuse with hippocampal atrophy, especially atrophy of the left hippocampus (Bremner et al., 1997; Stein, Koverola, Hanna, Torchia & McClarty, 1997). A recent meta-analysis of MRI findings in PTSD lends support to such findings (Kitayama, Vaccarino, Kutner, Weiss & Bremner, 2005). Such findings are of note given that the presence of severe childhood abuse (usually sexual, but also emotional) has been detected in approximately 50% of BP individuals across three separate studies (Garno, Goldberg, Ramirez & Ritzler, 2005; Hyun, Friedman & Dunner, 2000; Leverich et al., 2002). Unfortunately, only one study has considered whether childhood abuse impacts on neuropsychological dysfunction in BP (Savitz et al., 2008). Childhood Trauma Questionnaire (CTQ) sexual abuse scores were associated with impairments in visual memory, verbal learning, and cognitive inflexibility. CTQ emotional abuse scores were associated with executive dysfunction, including poor verbal fluency, and cognitive inflexibility (Savitz et al., 2008). The contribution of past childhood abuse to cognitive functioning in adult BP requires further attention.

Although childhood abuse is often associated with ADHD, this area of research has been understudied. In a study by Rucklidge, Brown, Crawford, & Kaplan (2006), emotional abuse and neglect were more common among men and women with ADHD as compared to controls. Sexual abuse and physical neglect were more commonly reported by females with ADHD relative to controls. Whereas Ford et al. (1999) found that a significant number of children with ADHD had a history of victimization (32%) trauma, a 4-year prospective study determined that children identified with ADHD were not at a higher risk for a traumatic experience than a comparison group (Wozniak et al., 1999). Unfortunately, there appear to be no studies that have considered the impact of childhood abuse on neuropsychological functioning in ADHD.

Medication. It is well known that many psychotropic medications can impact on cognitive performance. Neuropsychological studies of clinical groups should consider whether cognitive effects are due to medication type, medication doses, or the presence of multiple medications (Balanza-Martinez et al., 2010). The results of a recent review (Balanza-Martinez et al., 2010) suggest that most neuropsychological studies of BP assess individuals while they are taking a combination of medications, including mood stabilizers (lithium or anticonvulsants), antipsychotics, antidepressants, and/or benzodiazepines. Two reviews (Honig et al., 1999; Pachet & Wisniewski, 2003) concluded that within BP populations, lithium may exert mild negative effects on verbal memory and processing speed, while visuo-spatial, attentional and executive performance may be spared. Anticonvulsant medications including Valproic acid (valproate) and Carbamazepine seem to be associated with mild impairments in attention and memory (Balanza-Martinez et al., 2010). Lamotrigine, a new generation anticonvulsant, has been associated with significantly better performances on tests of verbal fluency and short-term verbal memory relative to Carbamazepine or Valproate (Daban et al., 2006). In a study which compared the

neurocognitive effects of six different medications in BP participants, Topiramate (an additional new generation anticonvulsant), Valproate and Carbamazepine were associated with the worst cognitive profiles, whereas Lamotrigine and Oxcarbamazepine (a classic anticonvulsant) had the least impact on cognition, and lithium was intermediate (Gualtieri and Johnson, 2006).

Most information regarding the neurocognitive effects of antipsychotic treatment in BP has been obtained from schizophrenia research. In a recent meta-analysis of the neurocognitive effects of various clinical variables in BP populations, studies that had reported a higher percentage of antipsychotic usage found larger effect size impairments for processing speed and sustained attention (Bora et al., 2009). The relatively large-scale Maudsley Bipolar Disorder Project found that antipsychotic usage among euthymic phase BPI individuals was correlated with deficits in verbal memory and verbal working memory (Donaldson, Goldstein, Landau, Raymont, & Frangou, 2003), as well as wide-spread executive dysfunction (Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005). At present it is unclear whether poorer neuropsychological outcomes are associated with atypical antipsychotics and/or conventional antipsychotics. Direct comparison of both classes is limited to one naturalistic study which found that euthymic phase BP individuals receiving atypical risperidone performed significantly better on a test of cognitive flexibility, and had a better occupational outcome than those taking conventional antipsychotics (Reinares et al., 2000). In terms of the atypical antipsychotic medications, only one randomized, double-blind study has investigated the neurocognitive effects of two different medications. Initiation of risperidone treatment was associated with better global cognition, fewer immediate cognitive adverse events and less cognitive fatigue when compared with quetiapine (Harvey et al., 2007).

Meta-regression analyses conducted by Bora et al. (2009) revealed that antidepressant use in BP was associated with processing speed difficulties and sustained attention problems. In patients with major depressive disorder, tricyclic antidepressants have been associated with impairments in verbal learning and memory (Amado-Boccaro, Gougoulis, Littre, Galinowski, & Loo, 1995) whereas selective serotonin reuptake inhibitors (SSRIs) and other non-tricyclic agents virtually lack cognitive adverse effects, and certain SSRIs may even improve working memory performance (Zobel et al., 2004). Finally, the detrimental cognitive effects of benzodiazepines and anticholinergic drugs are well-documented. In non-BP populations, the acute use of benzodiazepines is associated with anterograde amnesia (disability to learn new information), diminished attention, and psychomotor slowing (Buffett-Jerrott and Stewart, 2002). Indeed, long-term treatment has been associated with persistent cognitive impairments (Paterniti, Dufouil, & Alperovitch, 2002). In BP, exposure to benzodiazepines has been associated with lower performance on tasks of motor speed, processing speed and set-shifting (Martino et al., 2008).

The primary clinical intervention for ADHD over the past 50 years has been stimulant medication (see Spencer et al. (1996) for a review). There is a great deal of evidence that cognitive deficits involving certain executive functions (processing speed, inhibition), psychomotor speed, attention, and short-term memory, can improve with stimulant treatment (Berman, Douglas, & Barr, 1999; Loiser et al., 1996; Musten, Firestone, Pisterman, Bennett, & Mercer, 1997; Rapoport, Buchsbaum, & Weingartner, 1980). Newer non-stimulant treatments such as atomoxetine have also shown promise (Spencer et al., 1998).

Disease course factors relevant to bipolar disorder. The chronicity of BP, defined as illness duration, may predispose affected individuals to experience neuropsychological problems through fostering progressive frontal lobe damage or the disruption of frontal or subcortical circuits or fronto-mesolimbic circuits (Van Gorp et al., 1998). In some studies,

duration of illness has been associated with impairments in sustained attention (Clark, Iverson & Goodwin, 2002) and in processing speed (Bora et al., 2007). Nevertheless, two meta-analyses (Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011) found that illness duration did not result in poorer neuropsychological test performance among euthymic phase BP adults. In the meta-analysis conducted by Bora et al. (2009), younger age of illness onset was associated with larger effect sizes for measures of verbal learning and sustained attention. Indeed, most studies have failed to detect an effect of age at onset for other cognitive measures (Broadhead & Jacoby, 1990; Depp et al., 2004; Deckersbach et al., 2004; Thompson et al., 2005; Wylie et al., 1999;).

In BP populations, it is difficult to reliably ascertain whether the number of depressive or manic episodes has an effect on cognitive function as most studies have simply asked individuals to count the number of episodes retrospectively (Kessing, 1998). Indeed, BP individuals, family members, carers and doctors may forget moderate episodes and perhaps even severe episodes (Kessing, 1998). Moreover, the most impaired BP individual's may presumably forget the most episodes (Kessing, 1998). The number of episodes of lifetime mania has been associated with cognitive inflexibility (Van Gorp et al., 1998; Zubietta, et al., 2001) and impairments in verbal memory and learning (Cavanagh et al., 2002; Deckersbach et al., 2004; Martinez-Aran et al., 2004;). While one study reported a relationship between the number of manic episodes and impairment on a visual memory task (Deckersbach et al., 2004), two additional studies failed to detect this association (MacQueen, Young, Galway & Joffe, 2001; Rubinsztein, Michael, Paykel & Sahakian, 2000). Among BP populations, the number of episodes of lifetime depression has been associated with general cognitive decline (Kessing, 1998), difficulties with sustaining attention (Clark et al., 2002), cognitive inflexibility (Zubietta et al., 2001), and poor verbal memory (Deckersbach et al., 2004).

Non-clinical factors that may impact on cognitive functioning.

Age at testing. Neuropsychological research needs to carefully consider the effects of age as the development of many cognitive functions is maturational and relatively independent of social learning, although training may enhance their expression and aging ultimately tends to dull it (e.g. executive functions, memory, psychomotor speed) (Lezak, 2004). As demonstrated in a previous section (refer to The Contribution of Lifetime Comorbid ADHD to Neuropsychological Functioning in Bipolar Disorder section), the pattern of neuropsychological impairment observed in adult BP is similar to that observed in child/adolescent BP. With regard to older samples, Friedman et al. (1977) reported that euthymic phase BP individuals aged ≥ 59 yr performed poorer than younger individuals with BP on a comprehensive cognitive testing battery (Halstead–Reitan index). Clearly, longitudinal studies are required in order to better understand the cognitive impact of age on BP.

As described in a previous section (refer to The Contribution of Lifetime Comorbid ADHD to Neuropsychological Functioning in Bipolar Disorder section), the impairments in attention, executive functioning, and memory that were observed in adult ADHD were largely consistent with those described in the child/adolescent ADHD literature. Similar results have also been derived from a qualitative review (Woods, Lovejoy, Stutts, Ball, & Fals-Stewart, 2002). In terms of neuropsychological functioning in ADHD, Seidman (2006) points out that there is limited data on children under the age of 5, teenagers from age 13-18, and adults over the age of 40.

Premorbid intelligence and years of education. It is widely understood that years of education and intelligence play an important role in predicting performance across almost all tests that involve cognitive abilities (Lezak, 2004). Based on the findings of meta-analytic research, it is unlikely that premorbid IQ (Kurtz & Gerraty, 2009; Torres et al., 2007) and years of education (Bora et al., 2009) will vary significantly between the control and BP

groups in the present study. Meta-analytic research conducted with euthymic phase BP adults has associated IQ with inhibition (Bora et al., 2009) and years of education with less impairment on measures of auditory working memory and cognitive flexibility (Kurtz & Gerraty, 2009). It is possible that education may have a protective effect against specific forms of executive dysfunction in BP though further research is needed (Kurtz & Gerraty, 2009). Across a range of cognitive domains, Mann-Wrobel et al. (2011) found that the degree of neuropsychological impairment decreased as level of education increased in adults who have euthymic phase BP.

Given that ADHD is associated with long-standing cognitive difficulties, current rather than premorbid IQ has typically been employed to gauge levels of intellectual functioning. There is continuing debate in the current literature as to whether executive functioning data should be corrected for overall IQ level (Denckla, 1996). Especially in children with ADHD, many researchers have noted a correlation between executive functioning and IQ (Ardila, Pineda, & Rosselli, 2000), indicating at least a relation between the two. Other researchers (e.g. Nigg, 2001) have argued that controlling for IQ might remove some of the variance that is related to ADHD. A meta-analysis found that if factors known to moderate IQ in ADHD adults are absent (less years of education, few exclusionary criteria including the presence of comorbid Axis I disorders, especially learning disorders, and/or a history of head trauma, or neurological problems), the diagnosis of ADHD in and of itself should not warrant the controlling for or covarying of IQ in neuropsychological research (Bridgett & Walker, 2006). In the meta-analysis by Martinussen et al. (2005) which considers short-term verbal and spatial memory as well as verbal and spatial working memory, IQ did not explain group differences. Wilcutt et al. (2005) also continued to detect a range of neuropsychological differences after controlling for IQ. Covarying years of education is also debatable given that lower educational attainment is considered a hallmark consequence of ADHD (Barkley,

1998). It is unclear whether years of education can significantly account for group differences on measures of neuropsychological functioning in ADHD. In the Hervey et al. (2004) meta-analysis, the difference between years of education among the ADHD and control groups was 0.7 years.

Sex. Although controversial, research conducted with healthy participants has demonstrated sex differences in specific cognitive domains. Whereas there is a trend for females to perform better on verbal skills tasks, and often on measures that involve psychomotor speed (Majeres, 1988, 1990; Schmidt et al., 2000), males tend to perform better on predominantly non-verbal visuospatial tasks (Coltheart, Hull, & Slater, 1975). In the meta-analysis by Kurtz and Gerraty (2009), a larger percentage of male samples was associated with smaller effect size impairment on one measure of cognitive flexibility (Kurtz & Gerraty, 2009). Conversely, across a range of cognitive domains, Mann-Wrobel et al. (2011) found no significant relationship between sex and neuropsychological impairment in adults who have euthymic phase BP.

Although ADHD has an impact on both genders, most of the research literature, including studies evaluating cognitive performance, has been devoted to males (Berry, Shaywitz, & Shaywitz, 1985; Gaub & Carlson, 1997). The review by Seidman (2006) concluded that executive dysfunctions are correlates of ADHD regardless of gender. While a meta-analysis found that gender differences were not evident on measures of psychomotor skills, a more recent study failed to find gender differences on a measure of attention (Newcorn et al., 2001). Because most neuropsychological research into ADHD has focused on executive functioning, it is unclear whether gender differences among ADHD individuals exist in other neuropsychological domains such as memory.

Ethnicity. Ethnicity generally refers to groups that have a common nationality, religion, language or culture. While ethnicity can be associated with group differences on cognitive tests, like race, it is not an explanatory variable in itself (Lezak, 2004). For example, a study conducted in New Zealand found that Maori scored more poorly on tests that rely heavily on formal western education and concepts, and scored as well as or better than white New Zealanders on tests that that rely on concepts valued by Maori, including visuo-spatial skills (Ogden, Cooper, & Dudley, 2003). For a review of some of the factors postulated to underlie ethnic differences in cognitive functioning (particularly intellectual functioning), refer to Suzuki and Valencia, 1997).

Socio economic status. Socioeconomic status (SES) is strongly associated with cognitive ability and achievement during childhood and beyond (Noble, Norman, & Farah, 2005). Although SES is most commonly measured using occupation and income (Ensminger & Fothergill, 2003), in reality many other factors, including physical health, home environment, early education and neighborhood characteristics, vary systematically with SES and are likely to play a role in creating the SES gap in cognitive performance (Bornstein & Bradley, 2003). Language development has long been known to differ across SES (see Whitehurst, 1997, for a review). In a study of healthy children by Noble et al. (2005), SES differences were associated with disparities in performance in both the language and executive function systems, and with lesser disparities in visual cognition, visuospatial skills and memory.

Handedness. In determining patterns of cognitive functioning, the relative impact of handedness should be considered. Overall group tendencies for right-handers to perform better than left-handers on visuospatial tasks has been consistently observed (Bradshaw, 1989; Cerone & McKeever, 1999). According to Lezak (2004), spatial abilities among left-handers are more likely to be mediated in a diffuse manner by both hemispheres.

Nicotine and caffeine consumption. In addition to substance use disorders, neuropsychological studies should also consider the potential cognitive effects of nicotine and caffeine. Several studies have described the cognitive enhancing effects of acute nicotine administration in healthy volunteers (on measures of attention) (Barr et al., 2008), but particularly in individuals with schizophrenia (on measures of attention, spatial working memory, and inhibition) (Jacobsen et al., 2004; Barr et al., 2008). This is of note given that epidemiological and clinical studies indicate that the rates of smoking in individuals with BP are greater than the general population (Itkin, Nemets, & Einat, 2001; Ostacher et al., 2006). Nevertheless, a recent pilot study which included a wide ranging cognitive battery found no consistent differences in neuropsychological performance between two BP groups that were either current smokers or non-smokers (Law et al., 2009). There is evidence that cigarette smoking, which is also common among ADHD samples, may significantly improve performances on measures of inhibition (Potter & Newhouse, 2008). Indeed, cholinergic system activity may be important in the cognitive deficits of ADHD and may be a useful therapeutic target (Potter & Newhouse, 2008).

Neuropsychological research should also control for the potential cognitive effects of caffeine consumption. Evidence suggests that among normal populations, moderate levels of caffeine (about 75 mg) improve several aspects of cognitive performance including attention, reaction time, visual searching, psychomotor speed, memory, face recognition, and serial subtraction (Hewlett & Smith, 2006; Lieberman et al., 2002; Ryan, Hatfield, & Hofstetter, 2002; Scholey & Kennedy, 2004; Van Duinen, Lorist, & Zijdwind, 2005). While some investigators have posited that these improvements are due mainly to the reversal of withdrawal effects in caffeine-deprived participants (James, 1994; James & Keane, 2007), this notion is contested with some evidence suggesting otherwise (Christopher, Sutherland, & Smith, 2005; Hewlett

& Smith, 2006). It is unclear whether BP and ADHD samples demonstrate abnormal patterns of caffeine consumption.

Aims of the Present Study

In general terms, this study aims to clarify whether some of the neurocognitive impairments often detected in adult BP are partially the result of childhood ADHD.

Hypothesis one. It is postulated that young adult BP+childhood ADHD and ADHD-only groups will demonstrate similar yet significantly greater levels of executive dysfunction, verbal declarative memory impairment, and non-verbal memory deficits compared to young adult BP without childhood ADHD (BP-only) and control groups.

Hypothesis two. Among young adults, a BP-only group is likely to exhibit mild difficulties with sustaining attention relative to a control group. Young adult BP+childhood ADHD and ADHD-only groups are expected to be markedly and similarly compromised when it comes to sustaining attention relative to the BP-only and control groups.

Hypothesis three. On a measure of simple psychomotor speed, it is postulated that young adult BP+childhood ADHD, ADHD-only, BP-only and control groups will perform similarly.

CHAPTER 2: Sample and Methods

Overview of the Psychotherapy for Bipolar Disorder Study

Some background information will first be provided about the Psychotherapy for Bipolar Disorder Study (PBDS) because for the purposes of this thesis, two samples (a BP-only group and a BP+childhood ADHD group) were recruited from this larger study. The full project title for the PBDS was: A randomised clinical trial of interpersonal social rhythms psychotherapy in young people with bipolar disorder. The study was carried out by researchers from the Department of Psychological Medicine, University of Otago. The PBDS, which was funded by the Health Research Council of New Zealand, primarily aimed to establish whether psychotherapy, specifically interpersonal social rhythms therapy, may improve outcome, in individuals diagnosed with BP. BP individuals in the PBDS were randomly assigned to receive 18 months of either Interpersonal Social Rhythms Psychotherapy (IPSRT) or a “control” psychological treatment of Non Specific Supportive Clinical Management (NSCM). For comprehensive information about the aims and objectives of the PBDS, refer to the study’s information sheet in Appendix A. The PBDS consent and ethics approval forms are in Appendices B and C, respectively.

Recruitment for the PBDS occurred between 2003 and 2009. The 100 participants in the PBDS were from the Canterbury region in New Zealand, and were recruited by referral from mental health professionals and general practitioners, though some participants self-referred. The incentive to participate included an opportunity to receive free, high quality treatment over an 18 month period.

Participants

To be included in the present study, all participants were required to be aged 16 to 34 years and have English as a first language. Any individual was excluded if the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) detected the presence of severe alcohol or drug dependence as a principal diagnosis, or schizophrenia, or schizoaffective disorder. Similarly, individuals were excluded if the Physical Health Interview revealed a history of head injury with loss of consciousness exceeding 1 hour.

BP-only group. To be eligible to enter the BP-only group, individuals required a current diagnosis of DSM-IV defined BP (either BPI or BPII or BPNOS) based on the SCID-I. Individuals were excluded from this group if they met DSM-IV diagnostic criteria for ADHD as assessed by the Childhood Disorders Interview (CHILDDIS). The participants were identified from the larger sample of individuals diagnosed with BP, who were enrolled in the PBDS. The BP-only group consisted of 66 participants (48 females, 18 males). Whereas six participants identified as Maori (9.1%), 56 identified as New Zealand European (84.8%), and four identified as Other European (6.1%).

As mentioned above, participants were recruited into the PBDS from the Canterbury region in New Zealand. Referrals were from mental health professionals and general practitioners, though some participants self-referred.

ADHD-only group. For entry into the ADHD-only group, individuals required a current diagnosis of DSM-IV-TR defined ADHD (either ADHD Inattentive Type or Hyperactive/Impulsive Type or Combined Type) according to: 1) a summary based on the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID); 2) meeting the clinical cut-offs on the Conners' Adult ADHD Rating Scales (CAARS) Self-Report and Observer Forms (t-score's of at least 65 on four subscales: DSM-IV Inattentive Symptoms, DSM-IV Hyperactive-Impulsive Symptoms, DSM-IV ADHD Symptoms Total, ADHD Index); 3)

evidence of ADHD symptoms prior to the age of seven established either through a past diagnosis of ADHD or in newer cases, according to parental report and past school report cards. Individuals were excluded from this group if they had a history of meeting the DSM-IV diagnostic criteria for a manic or mixed episode based on the SCID-I.

Participants were recruited between 2007 and 2009, and were from the Canterbury region. The sample source included referrals from general practitioners, mental health professionals, and self-referral. Participants were also recruited from a database compiled by Associate Professor Julia Rucklidge at the University of Canterbury's ADHD Diagnostic Assessment and Research Unit. The database included clinical information and contact details for individuals that had previously been diagnosed with ADHD. As an incentive, each individual was informed that they would receive a psychological assessment summary based on their interview results and either a shopping voucher (\$25NZD Westfield Voucher) or a petrol voucher (\$25NZD MTA Voucher). Of the 27 (11 females, 16 males) individuals assigned to the ADHD-only group, 1 participant identified as Maori (3.7%), 22 (81.5%) identified as New Zealand European, and 4 identified as Other European (14.8%).

Two additional individuals who had been referred for potential inclusion in the ADHD-only group were not ultimately included. While a screening interview detected evidence of severe substance dependence in one individual, the research assessment found that another potential participant did not meet diagnostic criteria for ADHD.

BP+childhood ADHD group. Individuals were included in the BP+childhood ADHD group if they had a current diagnosis of DSM-IV defined BP (either BPI or BPII or BPNOS) based on the SCID-I, and a past childhood diagnosis of DSM-IV defined ADHD (either ADHD Inattentive Type or Hyperactive/Impulsive Type or Combined Type) as assessed by the CHILDDIS interview.

Sixteen of the participants were recruited from the PBDS. As mentioned previously, such participants were from the Canterbury region and referrals were from mental health professionals and general practitioners, though some participants self-referred. The BP+Childhood ADHD group consisted of 18 (10 females, 8 males) individuals of whom 2 were Maori (11.1%) and 16 were New Zealand European (88.9%).

Control group. To be eligible to enter the control group, the SCID-I had to confirm that individuals did not meet the DSM-IV diagnostic criteria for a current mood disorder or a lifetime manic or mixed episode. Individuals were also excluded from this group if scores were greater than 7 on either the Young Mania Rating Scale (YMRS) or the Montgomery and Asberg Depression Rating Scale (MADRS). Finally, individuals were excluded from the group if they had ever met the DSM-IV diagnostic criteria for ADHD as indexed by: 1) a record of past diagnoses including ADHD, obtained in CAADID Part II: History; 2) meeting the clinical cut-offs (t-score's greater than 64 on four CAARS sub-scales: DSM-IV Inattentive Symptoms, DSM-IV Hyperactive-Impulsive Symptoms, DSM-IV ADHD Symptoms Total, ADHD Index) on the CAARS Self-Report or Observer Forms.

Participants were recruited between 2007 and 2009, and were from the Canterbury region. Individuals were recruited through either advertisements in a local newspaper, or via a database compiled by Associate Professor Julia Rucklidge at the University of Canterbury's ADHD Diagnostic Assessment and Research Unit. The database included clinical information and contact details for healthy individuals that had no history of ADHD. As an incentive, each individual was informed that they would receive a psychological assessment summary based on their interview results and either a shopping voucher (\$25NZD Westfield Voucher) or a petrol voucher (\$25NZD MTA Voucher).

The control group consisted of 26 (16 females, 10 males) individuals. Whereas three participants identified as Maori (11.5%), a further three identified as Other European (11.5%). The remaining 20 participants (76.9%) identified as New Zealand European.

All of the participants who had been screened for potential inclusion in the control group were accepted.

Procedures

Procedure for the BP-only group and the BP+childhood ADHD group. The BP-only and BP+childhood ADHD (except for two participants) groups were recruited from the PBDS (a clinical trial which had received ethical approval from the Canterbury Ethics Committee in 2003). After individuals had been referred to the PBDS, they would be screened over the telephone by a research nurse. The research nurse established whether or not the referred individuals were likely to meet criteria for entrance into the study. Moreover, the research nurse provided information to the prospective participant about the nature of the research study.

If appropriate, individuals were then booked in to attend an initial clinical assessment by either the intended treating psychiatrist (or psychiatric registrar) at the Mental Health Clinical Research Unit (MHCRU). During this initial clinical assessment, a full psychiatric assessment was administered which included gaining information about BP symptomatology and related psychopathology. Individuals who were eligible for the PBDS were provided with verbal information about the study and given a written Information Sheet and the Consent Form (for copies of these forms, refer to appendices A and B, respectively). After providing written consent, PBDS participants were booked in at the MHCRU for a day of detailed research baseline assessment, lasting six hours (from 0900 until 1500). The baseline assessment included a biological assessment, self-report

questionnaires, neuropsychological assessment and structured clinical interviews. Only those assessments and information relevant to this thesis are presented here.

Participants in the PBDS were required to refrain from food and drink (including water) after 2300, the night before the baseline assessment. Throughout the baseline evaluation, participants were given a restricted water intake (500mls) and were asked to avoid caffeine or alcohol. During the morning of the baseline assessment, a psychiatrist administered a series of semi-structured interview measures. The present study considers data from six of these measures: SCID-I, MADRS, YMRS, Physical Health Interview, the Demographics Interview, and the Childhood Disorders Interview. The research nurse would then administer a number of self-report questionnaires. After 1100, a research assistant took individuals to a neuropsychological testing laboratory. In this laboratory, the research assistant administered the five minute long Neuropsychological Assessment Interview to gather background information pertinent to a neuropsychological evaluation. Two different neuropsychological tests were then administered: Facial Expression Recognition, which lasts for 20 minutes, and BiReme, which lasts for 30 minutes (for information about these two neurocognitive measures, refer to Appendix A). Data from both of these measures was not used in the present thesis. At 1300, following a 60 minute break, where refreshments had been provided, the research assistant administered a series of thirteen neuropsychological tests lasting 90 minutes (see Neuropsychological Testing Procedure below).

Data from many of the instruments that were administered are also relevant to this study as they helped to identify variables (covariates) which had the potential to impact on cognitive functioning. Specifically, data from the SCID-I also helped to determine clinical subtype (presence of BP-I, BP-II, or BP-NOS), comorbidity (presence of any current or lifetime anxiety disorder; any current or lifetime psychotic disorder; any current or lifetime alcohol or

substance abuse or dependence), and the presence of any past psychotic features. Three questions that were added to the SCID-I/P by investigators in the PBDS ask about the presence of any past child abuse (emotional, physical, or sexual) (refer to appendix G). These questions were only administered to participants in the BP+childhood ADHD and BP-only groups that were recruited through the PBDS. The SCID-I also identified variables that might account for differences between the BP and BP+childhood ADHD groups on measures of cognitive function: illness duration (calculated by subtracting age at first major depressive or manic mood episode from current age in years), age of BP onset (based on age at first mood episode), age of mania onset, age of depression onset, the presence of 10 or more manic episodes, and the presence of 10 or more depressive episodes.

Given that the severity of mania and depression symptoms can impact significantly on cognitive functioning, the present study also co-varied the total scores from the Young Mania Rating Scale and the Montgomery Asberg Depression Rating Scale, respectively. Information about whether individuals had experienced any significant learning difficulties during childhood was collected from the Physical Health Interview (refer to appendix H). The Neuropsychological Assessment Interview was drawn on to acquire information pertaining to medications used in the week preceding the cognitive assessment: any mood stabilizer, any antidepressant, any antipsychotic, any benzodiazepine, any stimulant, and the presence of medication from two or more drug classes (refer to appendix I). Information about the average number of daily caffeinated drinks consumed in the week preceding the cognitive assessment, and data about whether participants were current smokers, was also gathered during the Neuropsychological Assessment Interview. While information about total years of education was also obtained from this instrument, data from the National Adult Reading Test was used to consider the cognitive impact of premorbid IQ. This instrument was administered during the neuropsychological assessment. Data about demographic variables, including sex

(male, or female), and ethnicity which had the potential to impact on cognitive functioning, was obtained from the Demographics Interview.

Procedure for the ADHD-only group and the control group. Ethical approval to recruit participants for the ADHD-only and control groups was obtained from the Canterbury Upper South Ethics Committee (see Appendix D). The sample source included referrals from general practitioners, mental health professionals, and self-referral. Participants were also recruited from a database compiled by Associate Professor Julia Rucklidge at the University of Canterbury's ADHD Diagnostic Assessment and Research Unit. The database included clinical information and contact details for individuals that had previously been diagnosed with ADHD or were healthy. Advertisements in local newspapers were also used to recruit healthy participants for the control group. Once referrals were received, the primary investigator contacted potential participants by phone and informed them about the study and its aims. Individuals willing to participate in the study were booked in for a potential research assessment at the MHCRU.

Prior to the assessment, individuals willing to participate in the study received copies via the mail of the studies Information Sheet and Consent Form, as well as a note confirming their appointment time (for copies of these forms, refer to Appendices E and F, respectively). Such individuals were also asked to complete three questionnaires which had been sent out including: CAARS Self-report and Observer Forms, and the CAADID Part I: History. Given that the format of the research assessments for the ADHD-only and control groups varied, information about both research assessments is provided separately.

Research assessment for the ADHD-only group. Individual's referred for possible inclusion in the ADHD-only group, were assessed over two separate days with the first day lasting three hours and the second day lasting two hours. There was a one week gap between

the two assessment sessions. On arriving at the MHCRU, individuals were taken to an office where they were given the opportunity to review the studies Information Sheet and Consent Form, and ask any additional questions. Once written consent had been obtained, the primary investigator requested that any completed questionnaires (CAARS Self-report and Observer Forms, and the CAADID Part I: History) be handed in. The primary investigator then administered two 90 minute long semi-structured diagnostic interviews (CAADID Part II: Diagnostic Criteria; SCID-I) that were separated from each other by a 15 minute break, where refreshments were provided. Having administered the SCID-I, the primary investigator administered the 5 minute Physical Health Interview. At the end of the first assessment session, participants were asked to identify any primary school report cards so that they could be brought to the following session. If consent was granted, a person familiar to the participant (spouse, family member, or friend) was also contacted over the preceding week through the telephone for an interview. Questions were from the CAADID Part II: Diagnostic Criteria booklet, and they aimed to clarify whether the participant in the study exhibited ADHD symptoms during childhood.

Participants were required to refrain from taking stimulant medication for 48 hours prior to the second day of assessment. On arriving at the MHCRU for the second assessment session, participants were taken to a neuropsychological testing laboratory where the five minute Neuropsychological Assessment Interview was administered. A series of thirteen neuropsychological tests were then conducted, lasting 90 minutes (see Neuropsychological Testing Procedure below). After a 15 minute break, where refreshments were provided, two 15 minute semi-structured interviews were administered, which rated the severity of any manic (YMRS) or depressive (MADRS) symptoms.

Data from many of the instruments that were administered are relevant to this study as they involve variables (covariates) which have the potential to impact on cognitive functioning.

Specifically, data from the SCID-I also helped to determine comorbidity (presence of current anxiety disorder; current or lifetime alcohol or substance abuse or dependence), and the presence of past psychotic features. The CAADID Part I: History questionnaire was drawn on to establish whether individuals had experienced any past child abuse (emotional, physical, or sexual).

Given that the severity of mania and depression symptoms can impact significantly on cognitive functioning, the present study also co-varied the total scores from the YMRS and the MADRS, respectively. Information about whether individuals had experienced any significant learning difficulties during childhood was collected from the Physical Health Interview. The Neuropsychological Assessment Interview was drawn on to acquire information pertaining to medications used in the week preceding the cognitive assessment: any mood stabilizer, any antidepressant, any antipsychotic, any benzodiazepine, any stimulant, and the presence of medication from two or more drug classes. Information about the average number of daily caffeinated drinks consumed in the week preceding the cognitive assessment, and data about whether participants were current smokers, was gathered during the Neuropsychological Assessment Interview. While information about total years of education was also obtained from this instrument, data from the National Adult Reading Test was used to consider the cognitive impact of premorbid IQ. Data about demographic variables, including age, sex (male, or female), and ethnicity which had the potential to impact on cognitive functioning, was obtained from the CAADID Part I: History questionnaire.

Research assessment for the control group. Individual's referred for possible inclusion in the control group, were assessed during one session for three hours and thirty minutes. On arriving at the MHCRU, individuals were taken to an office where they were given the opportunity to review the studies Information Sheet and Consent Form, and ask any

additional questions. Once written consent had been obtained, the primary investigator requested that any completed questionnaires (CAARS Self-report and Observer Forms, and the CAADID Part I: History) be handed in. The primary investigator then administered the five minute Neuropsychological Assessment Interview, and a series of thirteen neuropsychological tests, lasting 90 minutes.

After a 15 minute break, where refreshments were provided, a 90 minute semi-structured diagnostic interview (SCID-I) was conducted as well as the 5 minute Physical Health Interview. Two, 15 minute semi-structured interviews were then administered, which rated the severity of any manic (YMRS) or depressive (MADRS) symptoms.

Data from many of the instruments that were administered are relevant to this study as they involve variables (covariates) which have the potential to impact on cognitive functioning. Specifically, data from the SCID-I also helped to determine whether any axis I disorders which had the potential to impact on cognitive functioning were present (presence of current anxiety disorder; current or lifetime alcohol or substance abuse or dependence). While the SCID-I also provided information about the presence of past psychotic features, the CAADID Part I: History questionnaire was drawn on to establish whether individuals had experienced any past child abuse (emotional, physical, or sexual).

Given that the severity of mania and depression symptoms can impact significantly on cognitive functioning, the present study also co-varied the total scores from the YMRS and the MADRS, respectively. Information about whether individuals had experienced any significant learning difficulties during childhood was collected from the Physical Health Interview. The Neuropsychological Assessment Interview was drawn on to acquire information pertaining to medications used in the week preceding the cognitive assessment: any mood stabilizer, any antidepressant, any antipsychotic, any benzodiazepine, any

stimulant, and the presence of medication from two or more drug classes. Information about the average number of daily caffeinated drinks consumed in the week preceding the cognitive assessment, and data about whether participants were current smokers, was gathered during the Neuropsychological Assessment Interview. While information about total years of education was also obtained from this instrument, data from the National Adult Reading Test was used to consider the cognitive impact of premorbid IQ. Data about demographic variables, including age, sex (male, or female), and ethnicity which had the potential to impact on cognitive functioning, was obtained from the CAADID Part I: History questionnaire.

Neuropsychological testing procedure for all groups. Cognitive testing took place in a laboratory within the MHCRU. All tests were administered according to standardised instructions. The six CANTAB subtests were administered through a CANTAB Eclipse touch-screen computer. A computer programme was used to present auditory information (i.e. word items) for trials one to seven of the Rey Auditory Verbal Learning Test (RAVLT). For the RAVLT recognition condition, each word was presented both verbally (through speakers) and visually (on a computer screen). For specific information about cognitive test administration times, and the order in which the tests were administered, refer to Table 1).

The present study included tests that pertained to four cognitive domains: psychomotor speed, sustained attention, verbal declarative memory, non-verbal memory, and executive functioning. In the present study, psychomotor speed was measured by considering response latencies on the CANTAB Motor Screening test. Outcome measures from two separate tests were used to assess sustained attention. Three outcome measures for the CANTAB Rapid Visual Information Processing test were considered: target sensitivity scores, the number of omission errors, and response latency. Total completion times for the Trail Making Test Part-A were also used to measure sustained attention.

For the verbal memory domain, short-term verbal memory was assessed by considering the total number of words correctly recalled on trial one of the RAVLT. The maximum number of digits correctly recalled on the Digit Span Forwards task was also considered. Verbal learning was assessed through considering total scores across trials one to five on the RAVLT. In evaluating long term verbal memory, the total number of words correctly recalled on trial eight of the RAVLT was considered. In measuring delayed verbal recognition memory, the percentage of items correctly identified on the recognition condition of the RAVLT was ascertained.

For the non-verbal memory domain, short-term visual object memory was assessed through two outcome measures from the CANTAB Delayed Matching to Sample test: percentage of correct responses across delays, and mean correct latency across all delays. In assessing short-term spatial memory, maximum span length on the CANTAB Spatial Span task was considered. Moreover, the results for two outcome measures from the CANTAB Spatial Recognition Memory test were considered: percentage correct, and mean correct latency.

This study examined five skills which are associated with executive functioning. Inhibition was measured through considering the total number of commission errors committed by participants on the CANTAB Rapid Visual Information Processing test. Cognitive flexibility was evaluated through considering completion times on the Trail Making Test Part-B. Spatial working memory was assessed through considering two outcome measures from the CANTAB Spatial Working Memory test: total number of between search errors (number of times a participant returns to search a box in which a token has already been found), and strategy scores (the ability of participants' to adopt a consistent search strategy). The maximum number of digits correctly recalled on the Digit Span Backwards test was used to evaluate verbal working memory. Verbal Fluency was assessed through considering the total number of words generated by participants on the Controlled Oral Word Association Test.

Table 1: *The order in which the neuropsychological tests were administered, and their respective administration times*

Cognitive assessment instrument	Administration time
Rey Auditory Verbal Learning Test (RAVLT) (trials one to seven)	10 mins
Motor screening (CANTAB)	3 mins
Spatial recognition memory (CANTAB)	5 mins
Delayed matching to Sample (CANTAB)	15 mins
RAVLT (trial 8)	1 min
RAVLT (recognition task)	5 mins
Trail making test	5 mins
Controlled Oral Word Association Test (COWAT)	5 mins
National Adult Reading Test (NART)	5 mins
Digit span (forward and backward)	5 mins
Spatial working memory (CANTAB)	15 mins
Spatial span (CANTAB)	8 mins
Rapid visual information processing (CANTAB)	8 mins
Total administration time:	90 mins

Measures

Clinical and demographic assessment measures.

Structured Clinical Interview for DSM-IV Axis I Disorders / Patient Edition (SCID-I/P) (First et al., 2002). The SCID-I/P is a semi-structured interview for assessing the major DSM-IV Axis I diagnoses. In the present thesis, all participants were administered the shortened version of the SCID-I/P employed by investigators in the PBDS. It included seven major sections: Mood Episodes, Mood Disorders, Psychotic and Associated Symptoms, Psychotic Disorders, Substance Use Disorders, Anxiety Disorders, and Eating Disorders. Investigators in the PBDS also incorporated supplementary questions about childhood abuse, self-mutilation, suicidal behaviour, and mood disorders. These supplementary questions were only administered to participants in the BP-only and BP+childhood ADHD groups. SCID-I/P assessment with a psychiatric individual usually takes between one and two hours, depending upon the complexity of past psychiatric history and the individual's ability to clearly describe episodes of current and past symptoms. SCID-I evaluation with a non-psychiatric individual usually takes between 30 and 90 minutes. The range in reliability of the SCID-I for DSM-III-R and DSM-IV is considerable, depending on the nature of the sample and research methodology (i.e., joint vs. test-retest, multi-site vs. single site with raters who have worked together, etc.). Kappa values reported for SCID-I BP diagnoses range from .79 (Skre, Onstad, Torgersen, & Kringlen, 1991) to .84 (Williams et al., 1992).

A considerable amount of data was extracted from the SCID-I/P. In the present study, dichotomous variables (yes/no) based on information from the SCID-I/P were used to ascertain whether a BP subtype was present (presence of BP-I, BP-II, or BP-NOS), and whether other specific lifetime or current diagnoses had also been present (current or lifetime anxiety disorder; current or lifetime alcohol or substance abuse or dependence; presence of

psychotic disorder). Using information obtained from the SCID-I/P, dichotomous variables were created which identified whether BP-only and BP+childhood ADHD group participants had experienced psychotic symptoms, 10 or more depressive episodes, and/or 10 or more manic episodes. A dichotomous variable which identified whether participants in the BP+childhood ADHD and BP-only groups had experienced child abuse was also developed. The variable was based on information obtained from three supplementary questions that had been incorporated into the SCID-I/P and which asked about the presence of childhood emotional, sexual, and physical abuse, respectively (refer to Appendix G to see an outline of these supplementary questions). Using data from the SCID-I, some clinical information was converted into continuous variables: the number of hospitalisations, illness duration (calculated by subtracting age at first major depressive or manic mood episode from current age in years), age of BP onset (based on age at first mood episode), age of mania onset, and age of depression onset.

Childhood Disorders Interview (CHILDDIS). The CHILDDIS is a semi structured interview applied to adults which aims to identify whether four different DSM-IV disorders of childhood were present during childhood: ADHD, overanxious disorder, separation anxiety disorder, and oppositional defiant disorder. While the CHILDDIS was administered in full to participants in the BP+childhood ADHD and BP-only groups, the present study only considered data from the ADHD section. The CHILDDIS was developed for use in the PBDS and its question format is derived from Merikangas et al. (1998) modified version of the Schedule of Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) (Endicott & Spitzer, 1978). The question format is broadly similar to that employed in the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman, Birmaher, Brent, Rao, & Ryan, 1996) which has good test-retest reliability for ADHD (.63) (Kaufman et al., 1997). Unlike the K-SADS-PL however,

information obtained in the CHILDDIS is obtained through self-report rather than through multiple informants. It also only provides information about lifetime diagnoses of ADHD whereas the K-SADS-PL provides information about both current and lifetime diagnoses.

Using information from the CHILDDIS, dichotomous variables were generated to determine whether three ADHD subtypes were present in individuals with BP recruited from the PBDS: ADHD-combined type, ADHD- predominantly inattentive type, or ADHD-predominantly hyperactive-impulsive type. The ADHD component of the CHILDDIS can be referred to in Appendix J.

Physical Health Interview (PHYHLTH). The PHYHLTH is a semi-structured interview which provides information about physical health. Specifically, it screens for the presence of head injuries, vision disturbances, childhood learning difficulties, and mood problems following general anaesthetics. It also includes questions about migraines based on the International Headache Society diagnostic criteria for Migraine With and Without Aura. The PHYHLTH takes five to ten minutes to administer and all responses are scored according to a yes/no format (e.g. “Have you ever had a serious head injury”). The Physical Health Interview was also developed for use in the PBDS.

Using information obtained from the PHYHLTH, dichotomous variables were created which identified whether participants across all groups had significant learning difficulties. This instrument was also used to exclude participants based on the presence of a head injury. This instrument was administered to all participants. As the PHYHLTH is not a standardised assessment, it can be referred to in Appendix H.

Conners’ Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein, Johnson, & Conners’, 2000). The CAADID is a semi-structured interview that assists in the process of diagnosing adult ADHD. The interview is divided into Part I and Part II, which are

administered separately. Each part requires approximately 90 minutes to complete. The CAADID Part I: History booklet was administered to the ADHD-only and control groups. It can be administered as a clinical interview or as a self-report questionnaire. It asks about various demographic and clinical variables, including age, family background, and different risk factors (gestational, delivery, temperamental, developmental, environmental, and medical). Other variables which are considered include child abuse, educational outcomes, occupational and interpersonal history, health and psychiatric history. The CAADID I: History booklet also includes a record of previous medications and doses as well as various comorbidity screening questions. The CAADID Part II: Diagnostic Criteria booklet is presented in interview format and was only administered to those referred for the ADHD-only group. It includes questions pertinent to an ADHD diagnostic assessment including questions about ADHD symptomatology (during childhood and adulthood), age of onset, pervasiveness, and level of impairment for any ADHD symptom that is indicated. Kappa values for overall diagnosis, which included all DSM-IV symptoms, were fair for both current (adult) ADHD diagnosis ($\kappa = .67$) and childhood report ($\kappa = .69$) (Epstein & Kollins, 2006).

Using information obtained from the CAADID Part I: History, a dichotomous variable was developed which identified whether participants in the ADHD-only and control groups had experienced abuse prior to the age of 16. The variable was based on information obtained from three questions that asked about the presence of childhood emotional, sexual, and physical abuse, respectively. Further dichotomous variables were based on information from CAADID Part I: History: sex (male, or female), and ethnicity (Maori, New Zealand European, Other European, Asian). Information obtained from CAADID Part I: History about age was incorporated into a continuous variable. Using information from Part I and Part II of the CAADID (as well as information from other sources), dichotomous variables were

created that determined whether three ADHD subtypes (ADHD-combined type, ADHD-predominantly inattentive type, or ADHD-predominantly hyperactive-impulsive type) were present in individuals who had consented to being assessed for possible entry into the ADHD or control groups.

Conners' Adult ADHD Rating Scales (CAARS) (Conners, Erhardt, & Sparrow, 1999). The CAARS quantitatively measure the presence and severity of ADHD symptoms across clinically significant domains, while examining the manifestations of those symptoms. The CAARS provide a multiple-informant assessment with self-report (CAARS-S) and observer forms (CAARS-O). Both types of CAARS form include 66 items, each rated on a scale from 0 to 3. On each form, there are four DSM-IV ADHD subscales including: DSM-IV Inattentive Symptoms, DSM-IV Hyperactive-Impulsive Symptoms, DSM-IV Total ADHD Symptoms, and ADHD Index. The CAARS forms also include an Inconsistency Index and various factor-derived subscales such as: Inattention/Memory Problems, Hyperactivity/Restlessness, Impulsivity/Emotional Lability, and Problems with Self-Concept. Cronbach's alpha across age, subscales and forms for men range from 0.61 to 0.91 and for woman range from 0.49 to 0.90 (Conners' et al., 2003). Using information from the CAARS, (as well as information from other sources), dichotomous variables were created that determined whether three ADHD subtypes were present in individuals who had consented to being assessed for possible entry into the ADHD-only or control groups. The CAARS was only administered to those referred for the ADHD-only and control groups.

Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978). The YMRS is an 11 item clinician rated scale, which measures the severity of mania. While 7 items are coded on a 0 to 4 scale (sleep, language/thought disorder, etc), 4 items are coded on a 0 to 8 scale (irritability, speech, thought content, etc). The YMRS has been used fairly often with adult populations, and it has accumulated good evidence of reliability and validity

(Young, 1978; Double, 1990). When it was developed, there was a high correlation between the scores of two independent clinicians on both the total score (0.93) and the individual item scores (0.66 to 0.92). Indeed, scores have been shown to correlate highly with an independent global rating, and with scores of two other mania rating scales administered concurrently (Young et al., 1998). The YMRS was administered to all participants.

Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). The MADRS is a clinician rated depression severity scale consisting of 10 items each rated on a scale from 0 to 6 (apparent sadness, inner tension, etc). The MADRS was specifically designed to provide a sensitive measure of depression severity, particularly for change during treatment. It has fewer somatic items than other depression rating scales (e.g. the Hamilton Depression Rating Scale) and has clear, wide-ranging definitions of its items and the scale steps. Overall the MADRS has been shown to have very good inter-rater reliability and sensitivity to change over time (Korner et al., 1990; Montgomery & Asberg, 1979). It was administered to all participants.

Neuropsychological Assessment Interview (NEUROPSYCH). The NEUROPSYCH is a semi-structured interview which seeks to obtain demographic and clinical information relevant to a neuropsychological investigation. It is used to gather information about handedness (left, right, or ambidextrous), years of education, level of confidence with computers (using a scale of one to five with one being “none” and five being “high”), and the presence of current medical illnesses. It is also drawn on to collect information about the average number of daily caffeinated drinks consumed in the week preceding the cognitive assessment, and about whether one is a current cigarette user. The NEUROPSYCH interview can also be employed to provide information about the type and dose of any current medications consumed by participants in the seven days leading up to a neuropsychological

assessment. The NEUROPSYCH takes five to ten minutes to administer and was also developed specifically for use in the PBDS. It was administered to all participants.

Using information obtained from this instrument, 10 dichotomous yes/no variables were created for the purposes of the present study: handedness (left, right, or ambidextrous), cigarette smoker, medication (any mood stabilizer, any antidepressant, any antipsychotic, any benzodiazepine, any stimulant, and the presence of medication from two or more drug classes). Some information was also converted into continuous variables: sum of secondary and tertiary years of education, and the number of caffeinated drinks typically consumed in the week preceding the assessment. As the NEUROPSYCH is not a standardised assessment, it can be referred to in Appendix I.

Demographics Interview (DEMO). This semi-structured interview is designed to collect demographic information about ethnicity, age, marital status, and number of children. This instrument was also developed for use in the PBDS, and it only takes a few minutes to administer. It was only administered to the BP with and without childhood ADHD groups. For the purposes of this thesis, age was treated as a continuous variable whereas dichotomous (yes/no) variables were used for sex (male, or female) and four different ethnic groups (Maori, New Zealand European, Other European, Asian).

National Adult Reading Test 2nd Edition (NART) (Nelson & Willison, 1992). The NART is used as a test of pre-morbid verbal IQ, as vocabulary correlates best with overall ability levels and tends to resist the degenerative processes better than other tests of intellectual attainment. The NART list comprises of 50 phonetically irregular words which participants are instructed to pronounce as accurately as they can. One year test retest coefficients are high (.89) (Deary et al., 2004), and although reliability is lower with longer re-test intervals (e.g. over four years), it is still respectable (.67 to .72) (Deary et al., 1998;

Kondel et al., 2003). In a review conducted by Strauss, Sherman, and Spreen (2006), it was concluded that the NART was a relatively good predictor of VIQ and FSIQ, but was relatively poor at predicting PIQ.

Measures of neuropsychological function.

Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1997). The RAVLT was employed to assess the short term storage of verbal information (immediate recall total score), verbal learning (total learning score), delayed verbal memory (delayed recall total score), and retrieval (recognition total score of List A). For the immediate recall and delayed recall conditions, each total score ranges from 0 to 15. Whereas the total learning score can range from 0 to 75, a percentage correct score is given for the recognition total score of List A. The RAVLT involves the auditory presentation of a list of 15 non-related words over 5 acquisition trials, followed by recall after each trial. A second distractor list of 15 different non-related words is then presented, and immediately after recall of this list, a sixth recall trial of the first list follows. After 20 minutes (during which other tasks are completed), a computer automated recognition condition is administered, and then delayed recall of the first list is tested. Reliability for the Rey varies from .38 for recall of List B to .70 for List A (Snow, Tierney, Zorzitto, Fisher, & Reid, 1988). For a one year interval between testing, a moderate finding of 0.55 has been found (Snow et al., 1988).

A history of lifetime ADHD may contribute to impaired verbal declarative memory in BP as meta-analytic effects on the RAVLT as well as the CVLT, a variant of this list learning paradigm, are similar among adult BP (Arts et al., 2008; Bora et al., 2009; Kurtz & Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007) and adult ADHD (Schoechlin & Engel, 2005; Hervey et al., 2004) populations. Such meta-analytic research suggests that list learning paradigms are the most sensitive to impairments in verbal declarative memory among BP and

ADHD populations. Unfortunately, no controlled studies have used the RAVLT to assess verbal declarative memory in BP with and without lifetime ADHD. Nevertheless, it is notable that two child/adolescent studies have detected verbal declarative memory impairment in BP with comorbid ADHD groups, but not in BP-only or ADHD-only groups on the CVLT (McClure et al., 2005) and the list learning conditions of the Wide Range Assessment of Memory and Learning test (Rucklidge, 2006).

Digit Span (DS) (Wechsler, 1997). The DS subtest was employed to assess the short term storage of verbal information (total forward span length) and verbal working memory (total backwards span length). The Digit Span Test comprises of two different tests: digits forward and digits backward. Scores for the digits forward and digits backwards conditions can each range from 0 to 9. Both tests consist of 7 pairs of random number sequences that are read aloud by the examiner. For digits forward, participants are instructed to repeat the sequence exactly as it is presented, and for digits backwards, the sequence is to be repeated in exactly the reverse order. If correct, the sequences continue, increasing in length until a pair of sequences is failed or until a 9-digit sequence is completed correctly. Moderate levels of reliability were demonstrated for this task in a classic study by Blackburn and Benton (1957).

The digit span forwards test was used to ascertain whether a history of lifetime ADHD may contribute to impaired short-term verbal memory in BP. Indeed, small yet significant meta-analytic effects have been detected for this instrument in adult BP (Arts et al., 2008; Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006) as well as adult ADHD (Boonstra et al., 2005) and child/adolescent ADHD (Martinussen et al., 2005). Although no controlled studies have compared BP with and without lifetime ADHD groups on the digit span forward test, it is perhaps notable that one study failed to detect impairments on this test in BP after carefully controlling for lifetime ADHD (Torralva et al., 2010).

The digits backwards test was selected as a measure of verbal working memory as it has also been associated with similar meta-analytic effects across adult BP (Arts et al., 2007; Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Torres et al., 2007; Robinson et al., 2006) and adult ADHD (Boonstra et al. 2005) populations. Although no controlled studies have explicitly compared BP with and without lifetime ADHD on the digits backwards test, Torralva et al. (2010) also failed to detect impairments on this test in BP after carefully controlling for lifetime ADHD.

Trail Making Test (TMT) (Corrigan, & Hinkeldey, 1987). The TMT was drawn on to assess sustained attention (time taken to complete Part A) and cognitive flexibility (time taken to complete Part B). The TMT consists of two parts, Trails A (see below) and Trails B. It requires the connection, by making pencil lines, between 25 encircled numbers randomly arranged on a page in proper order (TMT-A) and of 25 encircled numbers and letters in alternating order (TMT-B). Whilst reliability coefficients vary considerably, most are above .60 but several are in the .90s (Spreeen & Strauss, 1998).

The TMT-A was selected as a measure of sustained attention as meta-analytic effects across adults with ADHD (Hervey et al., 2004; Boonstra et al., 2005) are similar to those detected in euthymic phase BP adults (Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006; Torres et al., 2007). Also, given that lifetime ADHD is associated with higher rates of mood episodes in BP (see Greater frequency of mood episodes section), it is notable that TMT-A performance is particularly poor in BP adults experiencing mixed/manic or depressed episodes (Kurtz & Gerraty, 2009). Only one other study has applied a paradigm similar to the TMT-A to determine whether lifetime ADHD contributes to sustained attention difficulties in BP. Using Color Trails 1, Rucklidge (2006) failed to detect any group differences in children/adolescents that had BP with and without lifetime ADHD. Nevertheless, the significance of this result is questionable as Color Trails 1

and the TMT-A have both been shown to be particularly vulnerable to age effects in healthy individuals (Lee & Chan, 2000; Maj et al., 1993). Also, it is notable that Torralva et al. (2010) failed to detect impairments on this test in BP adults after carefully controlling for lifetime ADHD.

A history of lifetime ADHD may contribute to impaired cognitive flexibility as indexed by the TMT-B in BP as meta-analytic effects for this measure are similar across adult BP (Arts et al., 2007; Kurtz & Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007; Bora et al., 2009; Mann-Wrobel et al., 2011) and adult ADHD (Boonstra et al., 2005; Hervey et al., 2004) samples. Also, meta-analytic research suggests that for ADHD in particular, TMT-B is more likely to be sensitive to cognitive inflexibility, relative to other tests, including the Wisconsin Card Sorting task. Although no controlled studies have explicitly compared BP with and without lifetime ADHD on the TMT-B, it is noteworthy that one study failed to detect impairments on this test in BP after carefully controlling for lifetime ADHD (Torralva et al., 2010).

Controlled Oral Word Association Test (COWAT) (Benton, Hamsher, & Sivan, 1994). The COWAT was employed to assess verbal fluency (total number of words named over the three, 60 second trials). Participants are instructed to produce as many words as possible beginning with a given letter in a 1 minute period. The letters F, A, and S are given as they are the most commonly used letters for this test. Excellent interrater reliability has been detected for this instrument (.90) in recent studies (Ross et al., 2007; Ross, 2003).

The COWAT was selected as a measure of verbal fluency as it has been associated with similar meta-analytic effects across adult euthymic phase BP (Arts et al., 2008; Bora et al., 2009; Robinson et al., 2006; Torres et al., 2007; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011) and adult ADHD (Boonstra et al., 2005; Hervey et al., 2004) as well as

child/adolescent ADHD populations. This study is unique in that it is the first to explicitly compare BP with and without lifetime ADHD on the COWAT.

Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB is a computer-based cognitive assessment system which is administered to participants through a touch screen computer. It assesses a variety of cognitive functions: general memory and learning, working memory and executive function, visual memory, attention and reaction time, semantic/verbal memory, decision making and response control. The five CANTAB tests incorporated into the present study are described in detail below. The CANTAB has been a widely used tool for evaluating cognitive functioning in a very wide variety of neuropsychological and psychiatric disorders (Lange et al., 1992; Muir, Everitt, & Robbins, 1995; Owen, Sahakian, Semple, Polkey, & Robbins, 1991; Robbins et al., 1994; Sahakian & Owen, 1992). For information about the test retest reliability for individual tests, refer to a review by Lowe and Rabbitt (1998). According to the review, reliability coefficients were satisfactory.

CANTAB Delayed Matching to Sample (DMS). The DMS test was drawn on to assess short-term visual-object recognition memory. Two outcome measures were drawn on: percentage correct across delays and average latency (in ms) to respond correctly across delays. Participants are shown a complex visual pattern (the sample) and then after a brief delay, four patterns are presented below the sample. Participants are instructed to touch the pattern that matches the sample. In some trials the sample and the choice patterns are shown simultaneously, whereas in other trials, a delay of 0, 4, or 12 seconds is introduced between covering the sample pattern and showing the choice patterns. A study detected a test-retest correlation of .56 for this test (Lowe & Rabbitt, 1998).

Although there are no controlled studies that have applied the DMS test to adults with ADHD, it is significant that children/adolescents with ADHD demonstrate significant impairment on this measure compared to controls (Kempton et al., 1990; Rhodes et al., 2005; Vance et al., 2003). In the three aforementioned studies, greater impairment was noted on the DMS test than on any other cognitive measure. Henceforth, it is plausible that this test in particular may help to differentiate a BP with comorbid ADHD group from a BP-only group.

It is plausible that undetected ADHD may account for findings of compromised DMS performance in BP across different mood states (Rubinsztein et al., 2006; Sweeney et al., 2000; Murphy et al., 1999). Indeed, only one study has failed to detect impaired DMS performance in a BP sample (Maalouf et al., 2010). At present there are no controlled studies that have explicitly compared DMS test performance in BP with and without lifetime ADHD groups.

CANTAB Spatial Span (SS). The SS subtest was used to assess the short-term storage of spatial information (span length). Scores range from 0 to 9. Nine white squares are presented on the screen and the squares change colour one by one, starting with a sequence of two. Participants then indicate the order in which the squares changed colour by touching them. Progressively more squares change colour (up to a possible 9) as sequences are correctly ordered.

Unfortunately, only two controlled studies have attempted to apply the SS test to adult ADHD. Whilst a trend for significance was detected in one of these studies (McLean et al., 2004), there was no evidence of impairment in the ADHD group in the other study (Gropper & Tannock, 2009). It may have been difficult to detect group effects in the Gropper and Tannock (2009) study because it included a high IQ ADHD sample which may have been associated with a rather mild symptom presentation. Regardless, it is notable that meta-

analytic research has detected significant effects on spatial span paradigms in children and adolescents with ADHD (Martinussen et al., 2005).

Studies which used the SS test but failed to control for lifetime ADHD comorbidity have consistently detected poorer performances in BP across different moodstates (Thompson et al., 2005; Roiser et al., 2009; Sweeney et al., 2000; Badcock et al., 2005). Unfortunately, no controlled studies have explicitly compared SS test performance in BP with and without lifetime ADHD groups.

CANTAB Spatial Recognition Memory (SRM). The SRM measure was employed to assess short-term recognition memory for spatial locations. Two outcome measures were used: percentage correct, and average latency (in ms) to respond correctly. After five squares are presented sequentially at different locations on the screen, participants are presented with a pair of squares in counterbalanced order. They are instructed to identify which square is at a location where one was previously presented. Four trials are held.

Given that only one controlled study of adults has drawn on the SRM test to assess for difficulties in sustained attention in ADHD populations, further research is warranted. No group differences were detected (McLean et al., 2004). Nevertheless, the SRM test may help to elucidate the contribution of ADHD to spatial memory impairment in BP as child/adolescent ADHD samples consistently demonstrate impairment on this measure relative to controls (Kempton et al., 1999; Rhodes et al. 2005; Vance et al. 2003).

Indeed, a history of undetected ADHD may account for findings of compromised performance on the SRM test in BP adults compared to controls (Thompson et al., et al., 2005; Rubinsztein et al., 2006; Sweeney et al., 2000; Murphy et al., 1999). With that being said, some studies have failed to detect impaired SRM performance in BP (Roiser et al., 2009; Braw et al., 2007). Whilst one study has attempted to compare BP with and without

lifetime ADHD groups on the SRM test, further research is required as the study in question had a number of methodological limitations. Although Dickstein et al. (2004) failed to detect significant differences between BP with current comorbid ADHD ($n = 12$) and BP without current comorbid ADHD subgroups ($n = 10$), the significance of this result is questionable as some participants in the latter group also had lifetime ADHD. In addition, the low sample sizes for these sub-groups may have made it difficult to detect significant effects.

CANTAB Rapid Visual Information Processing (RVP). In assessing visual sustained attention, consideration was given to three different scores on the CANTAB Rapid Visual Information Processing (RVP) subtest: total number of omission errors, average latency (in ms) to respond correctly, and overall target sensitivity (or accuracy). The range of scores for the target sensitivity measure range from 0.00 to 1.00 with lower scores indicating greater impairment. In assessing inhibition with the RVP test, the total number of commission errors was considered. During the RVP test, a white box is presented on the screen in which digits from 1 to 9 appear in a pseudo-random order at the rate of 100 digits per minute. Participants are instructed during the four minute testing phase to detect target sequences of digits (3-5-7, 2-4-6, and 4-6-8) and to register responses by pressing a response pad at the end of the target sequence.

Given that virtually no controlled study has drawn on the RVP test to assess for difficulties in sustained attention in ADHD populations, further research is warranted. In a study with small sample sizes, Chamberlain et al. (2007) found that the difference between an ADHD group and controls approached significance on the target sensitivity outcome measure. Also, there is evidence that medications known to target compromised neural strata in ADHD, including Methylphenidate (Elliot et al., 1997; Turner et al., 2005), and Modafinil (Randall et al., 2005; Turner, L. Clark, J. Dowson, T.W. Robbins, B.J. Sahakian), significantly enhance performance in ADHD samples. It is also noteworthy that significant meta-analytic effects

exist for adult ADHD using sustained attention outcome measures on alternative CPTs (Hervey et al. 2004; Boonstra et al., 2005). Each of the five controlled studies that applied the RVP test to BP populations detected impairments in sustained attention, especially on the target sensitivity outcome measure (Braw et al., 2007; Clark et al., 2001; Clark et al., 2005; Maalouf et al., 2010; Clark et al., 2002). This is consistent with the results of meta-analytic research which have employed alternative CPTs (Arts et al., 2009; Bora et al., 2009; Kurtz & Gerraty, 2009; Torres et al., 2007). At present there are no controlled studies which have explicitly compared RVP test omission error rates or target sensitivity in BP with and without lifetime ADHD groups.

Given that virtually no controlled studies have drawn on the RVP test to assess for inhibition difficulties in ADHD populations, further research is warranted. In a study with small sample sizes, Chamberlain et al. (2007) found that the difference between an ADHD group and controls approached significance on the commission errors outcome measure. Also, there was evidence that a drug (Atomoxetine) known to target compromised neural strata in ADHD significantly enhanced performance in this group (Chamberlain et al., 2007). Using a related outcome measure (probability of false alarm), a non-controlled study found that Atomoxetine also significantly enhanced performance in an ADHD sample (Gau & Shan, 2010).

Regardless, it is noteworthy that significant meta-analytic effects exist for adult ADHD using the commission error outcome measures of alternative CPTs (Hervey et al. 2004; Boonstra et al., 2005). Further research is also required in order to establish whether the RVP test is able to detect disinhibition in BP populations. At present only two controlled studies have considered RVP commission error rates in BP populations (Clark et al., 2002; Maalouf et al., 2010) and although neither study detected group differences, this is broadly inconsistent with the results of meta-analytic research which considered commission error rates on alternative CPTs (Boonstra et al., 2005; Hervey et al., 2004). This study is unique in that it is the first to

explicitly compare RVP test commission error rates in BP with and without lifetime ADHD groups.

CANTAB Spatial Working Memory (SWM). The SWM test was used to assess spatial working memory. Two outcome measures were used: total between errors and strategy score. Scores for the strategy score range from 8 to 56 with high scores representing poor use of strategy. The SWM test is a self-ordered searching task, whereby participants are asked to search through boxes on a computer screen to discover which one hides a coloured token. Task difficulty is manipulated by increasing the number of boxes presented in a block of trials (e.g., 4, 6, or 8). The ability of participants' to adopt a consistent search strategy is also evaluated. Two types of search error are also tabulated. For the purposes of this study two scores are tabulated. These include a strategy score and the number between search errors. A between search error occurs when one returns to search a box in which a token has already been found. A study detected a test-retest correlation of .68 for this test (Lowe & Rabbitt, 1998).

A history of lifetime ADHD may help to explain why spatial working memory impairment as measured by the SWM test is consistently detected in adult BP (Clark et al., 2002; Braw et al., 2007; Roiser et al., 2009; Badcock et al., 2005; Barrett et al., 2008; Thompson et al., 2005; Sweeney et al., 2000). Indeed, the SWM test is also particularly sensitive to impaired spatial working memory in ADHD as indexed by large effects in adult (Chamberlain et al., 2007; Dowson et al., 2004; McLean et al., 2004), and child/adolescent ADHD (Martinussen et al., 2005) using both the strategy and between search error outcome measures. Only one other study has attempted to compare BP with and without lifetime ADHD groups on the SWM test (Dickstein et al., 2004). Although the study failed to detect significant effects, it is noteworthy that neither group was compared to a control group and that the sample sizes of each subgroup were small (Dickstein et al., 2004). More importantly, it is significant that the

investigators considered the total search error outcome measure (which collapses together within and between search errors) as this has generally failed to detect impairment in other studies of ADHD (Dickstein et al., 2004).

Statistical Analyses

Statistical analyses were conducted with Statistical Package for the Social Sciences version 17 (SPSS, Inc., Chicago, Illinois). Prior to the primary analysis, neuropsychological data were tested for conformity to a normal distribution through giving consideration to skewness, kurtosis, and visual representations of the distributions. No data transformations were necessary. Using Wilks' Lambda as an overall test of significance ($< .05$), multivariate analysis of covariance (MANOVA) was employed to establish whether group differences existed within each of the five cognitive domains: motor speed, verbal declarative memory, nonverbal memory, attention, and executive functioning. For a cognitive domain, the Wilks' Lambda statistic needed to remain significant after co-varying variables which had the potential to impact on cognitive functioning (e.g. premorbid IQ). Such variables were only entered into the MANOVA if other analyses had demonstrated that they were unevenly distributed among the groups (see next paragraph). Specific group differences on cognitive measures were identified using Bonferroni post-hoc tests. Given the small sample size and low power available to detect group differences, effect sizes (Cohen's d) were calculated for all of the outcome measures.

Three different analyses were used to compare the groups on variables that had the potential to influence cognitive functioning. Each analysis used a significance level of $p < .05$.

Differences among the four groups on continuous clinical variables (e.g. depression severity) or continuous demographic variables (e.g. age at testing) were assessed with univariate analysis of variance (ANOVA) and post-hoc Bonferroni tests. Chi-square analyses were used

to examine differences among the four groups on dichotomous clinical variables (e.g. presence of lifetime anxiety disorder) or on dichotomous demographic variables (e.g. ethnicity). Independent-samples t-tests were also used to examine differences between the BP and BP+childhood ADHD groups on continuous clinical variables (e.g. depression onset).

CHAPTER 3: Results

The results section is divided into three subsections: (1) A description of the sample characteristics of the four groups; (2) group differences on variables that can impact on cognitive functioning; (3) a comparison of neuropsychological functioning i.e. psychomotor speed, non-verbal memory, verbal declarative memory, attention, and executive functioning across the four groups (ADHD-only, BP-only, BP+childhood ADHD, and control groups).

Sample Characteristics

Demographic characteristics. The samples demographic characteristics for the ADHD-only, BP-only, BP+childhood ADHD, and control groups are included in Table 2. There were no significant group differences in age or ethnicity. The four groups did differ significantly in terms of sex distribution with the BP-only group demonstrating a higher percentage of women compared to the ADHD-only group

Current Axis I mood disorders and mood severity. The BP-only and BP+childhood ADHD groups did not differ significantly in terms of the distribution of BPI, BPII, or BP NOS diagnoses (refer to Table 3). For information about the severity of mood symptomatology refer to Table 4. Depression, based on MADRS scores greater than 10, was present in 60.6% of the BP-only group, 44.4% of the BP+childhood ADHD group, and 25.9% of the ADHD-only group. The level of depression severity was significantly lower in the control group when compared to the BP-only, ADHD-only, and BP+childhood ADHD groups. The BP-only group was also more impaired relative to the ADHD-only group in terms of depression symptom severity. There was no evidence that any individual within the present sample was experiencing hypomania or mania as defined by YMRS total scores greater than 11. However, as expected, the level of mania severity was significantly lower in the control group compared to the ADHD-only, and BP+childhood ADHD groups. The

Table 2: Demographic characteristics of the ADHD-only, BP-only, BP+Childhood ADHD and control groups

	ADHD-only (n = 27)		BP-only (n = 66)		BP+childhood ADHD (n = 18)		Control (n = 26)				
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>F</i>	<i>df</i>	<i>p</i>
Age at testing	24.89	5.21	25.68	5.34	25.28	5.54	24.62	5.57	.30	3, 133	.82
	<i>N</i>	<i>%</i>	<i>N</i>	<i>%</i>	<i>N</i>	<i>%</i>	<i>N</i>	<i>%</i>	χ^2	<i>df</i>	<i>p</i>
Ethnicity									5.07	6, 137	.53
New Zealand European	22	81.5	56	84.8	16	88.9	20	76.9			
Other European	4	14.8	4	6.1	0	0	3	11.5			
Maori	1	3.7	6	9.1	2	11.1	3	11.5			
Sex									8.73	3, 137	.033
Male	16	59.3	18	27.3	8	44.4	10	38.5			
Female	11	40.7	48	72.7	10	55.6	16	61.5			

Table 3: Current primary and comorbid axis I psychiatric diagnoses in the ADHD-only, BP-only, and BP+childhood ADHD groups as well as current axis I psychiatric disorders in the control group

	ADHD-only (n = 27)		BP-only (n =66)		BP+childhood ADHD (n =18)		Control (n =26)				
	<i>n</i>	%	<i>N</i>	%	<i>n</i>	%	<i>N</i>	%	χ^2	<i>df</i>	<i>p</i>
Primary diagnoses											
Bipolar type									2.71	2, 84	.26
BP I	-	-	48	72.7	16	88.9	-	-			
BP II	-	-	15	22.7	1	5.6	-	-			
BP NOS	-	-	3	4.5	1	5.6	-	-			
ADHD type									6.59	2, 45	.037
Inattentive	10	37	-	-	5	27.8	-	-			
Hyperactive / Impulsive	0	0	-	-	4	22.2	-	-			
Combined	17	63	-	-	9	50	-	-			
Other current diagnoses											
Major depressive disorder	4	14.8	-	-	-	-	-	-	-	-	-
Any anxiety disorder	9	33.3	22	33.3	10	55.6	3	11.5	9.65	3, 137	.022
Any eating disorder	0	0	2	3.0	1	5.6	0	0	2.36	3, 137	.50
Any alcohol abuse / Dependence	3	11.1	2	3.0	1	5.6	1	3.8	1.76	3, 137	.63
Any other substance abuse /Dependence	0	0	5	7.6	3	16.7	0	0	7.49	3, 137	.058

Table 4: Severity of current mood symptomatology at testing in the ADHD-only, BP-only, BP+childhood ADHD, and control groups

	ADHD-only (n = 27)		BP-only (n = 66)		BP+childhood ADHD (n = 18)		Control (n =26)		<i>F</i>	<i>df</i>	<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>			
Montgomery Asberg Depression Rating Scale (total score)	8.19	4.84	14.85	10.5	13.61	9.13	1.15	2.28	18.21	3, 133	< .001
Young Mania Rating Scale (total score)	2.85	2.91	1.7	2.33	4.22	4.99	0.54	1.24	7.28	3, 133	< .001

BP+childhood ADHD group was also more impaired relative to the BP-only group in terms of mania symptom severity.

Current and childhood ADHD. The ADHD-only group had a lower percentage of Hyperactive/Impulsive Type ADHD compared to the BP+childhood ADHD group (refer to Table 3).

Other current Axis I disorders. Information about current Axis I disorders for the control group is included in Table 3 as is information about current comorbid diagnoses for the three clinical groups. The four groups differed significantly in terms of the presence of a current anxiety disorder. The control group had a lower percentage of current anxiety disorder compared to the BP-only and BP+childhood ADHD-only groups.

Other lifetime Axis I diagnoses. Information about lifetime Axis I diagnoses other than ADHD and BP is found in Table 5. The control group was less likely to have experienced a lifetime anxiety disorder compared to the BP-only, ADHD-only, and BP+childhood ADHD groups. The BP+childhood ADHD group was more likely to have experienced a lifetime anxiety disorder compared to the ADHD-only group. The BP-only group was more likely to have experienced a lifetime eating disorder compared to the ADHD-only and control groups. The BP+childhood ADHD group was also more likely to have experienced a lifetime eating disorder compared to the ADHD-only and control groups. The four groups did not differ significantly in terms of the presence of lifetime alcohol abuse or dependence. However, the control group was less likely to have experienced lifetime non-alcohol substance abuse/dependence and lifetime alcohol or substance use disorder compared to the BP-only, ADHD-only, and BP+childhood ADHD groups. A comparison was made between the ADHD-only group and the control group with regard to having ever experienced

Table 5: *The presence of lifetime axis I psychiatric diagnoses (excluding bipolar disorder and ADHD) in the ADHD-only, BP-only, BP+childhood ADHD, and control groups*

	ADHD-only (n = 27)		BP-only (n =66)		BP+childhood ADHD (n = 18)		Control (n =26)				
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	χ^2	<i>df</i>	<i>p</i>
Major depressive disorder	15	55.6	-	-	-	-	6	23.1	5.84	1, 53	.016
Any anxiety disorder	12	44.4	36	54.5	14	77.8	4	15.4	18.74	3, 137	< .001
Any eating disorder	0	0	11	16.7	6	33.3	1	3.8	13.20	3, 137	.004
Any alcohol abuse / Dependence	13	48.1	26	39.4	8	44.4	4	15.4	7.22	3, 137	.065
Any other substance abuse / dependence	8	29.6	23	34.8	9	50	0	0	15.51	3, 137	.001
Any alcohol / substance use disorder	13	48.1	33	50	11	61.1	4	15.4	11.89	3, 137	.008

a major depressive episode. More individuals in the ADHD-only group had experienced lifetime major depressive disorder compared to the control group.

Group Differences on Variables that can Impact on Cognitive Functioning.

In the previous section, significant group differences were detected for a number of variables known to have some impact on neuropsychological functioning: sex distribution, depression and mania severity, the presence of a current anxiety disorder, and the presence of a lifetime alcohol or substance use disorder. Although the distribution of ADHD subtypes varied significantly between the BP+childhood ADHD and ADHD-only groups, the presence of small sample sizes for some of these subtypes meant that ADHD subtype was not covaried.

This study also considers whether the four groups vary on other variables known to impact on cognitive function (see Table 6). Although a main effect was found for premorbid IQ, Bonferroni post hoc analyses failed to identify significant differences among the BP-only, control, BP+childhood ADHD, and ADHD-only groups. Moreover, the four groups failed to differ significantly in terms of years of secondary and tertiary education. The control group had a lower percentage of cigarette smokers when compared to the BP-only and BP+childhood ADHD groups. There were no significant differences among the four groups regarding the average number of daily caffeinated drinks consumed in the week preceding the cognitive assessment or in handedness.

The groups differed in terms of having experienced learning problems during childhood as detected by the Physical Health Interview and in the case of the ADHD-only and control groups, the CAADID History questionnaire as well. Specifically, the ADHD-only group had a higher percentage of childhood learning difficulties compared to the BP-only and control groups. The BP+Childhood ADHD group had experienced a higher percentage of past child abuse compared to the ADHD-only, control and BP-only groups. The BP-only group had also

Table 6: *Other clinical and nonclinical variables known to potentially impact on cognitive functioning in the ADHD-only, BP-only, BP+childhood ADHD, and control groups*

	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n = 18)		Control (n = 26)				
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	χ^2	<i>df</i>	<i>p</i>
Clinical											
Any childhood abuse	9	34.6	32	48.5	14	77.8	3	12.5	19.51	3, 134	<.001
History of Psychotic Symptomatology	1	3.8	38	57.6	11	61.1	0	0	44.12	3, 136	<.001
Any significant learning difficulties during childhood	11	42.3	9	13.6	4	22.2	1	3.8	14.15	3, 134	.003
Non-Clinical											
Right handed	22	81.5	60	90.9	16	88.9	22	84.6	1.84	3, 137	.61
Current smoker	7	25.9	28	42.4	8	44.4	3	11.5	10.03	3, 136	.018

Note: Table 6 continues on the following page.

Table 6 continued: *Other clinical and nonclinical variables known to potentially impact on cognitive functioning in the ADHD-only, BP-only, BP+childhood ADHD, and control groups*

	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n = 18)		Control (n = 26)				
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>F</i>	<i>df</i>	<i>p</i>
Average number of daily caffeine drinks	1.81	1.94	2.86	3.68	3.53	2.65	1.5	1.39	2.53	3, 132	.060
Years of secondary and tertiary education	6.59	2.06	6.44	2.60	5.67	2.22	7.35	2.23	1.83	3, 133	.14
NART Predicted Verbal IQ	100.41	8.55	105.17	7.83	101.44	9.13	105.85	8.26	3.158	3, 133	.027

experienced a higher percentage of child abuse relative to the control group. A higher percentage of participants in the BP+childhood ADHD and ADHD-only groups had experienced psychotic symptoms compared to those in the ADHD-only and control groups.

Information about group differences in medication consumption can be found in Table 7. As expected, a higher percentage of participants in the BP+childhood ADHD and BP-only groups had consumed mood stabilizer, antidepressant, and antipsychotic medication in the week prior to the assessment compared to those in the ADHD-only and control groups. Nonetheless, a higher percentage of participants in the ADHD-only group had also consumed antidepressant medication compared to those in the control group. As expected, a higher percentage of participants in the ADHD-only group had consumed stimulant medication compared to those in the BP-only and control groups. There were no significant group differences with respect to benzodiazepine medication consumption in the week preceding the cognitive assessment. As expected, a higher percentage of participants in the BP+childhood ADHD group and BP-only groups had consumed medication from two or more drug classes compared to those in the ADHD-only and control groups.

The presence of potential disease course covariates that were particularly relevant to the BP-only and BP+childhood ADHD groups was also considered (see Table 8). An independent-samples t-test showed that the average duration of BP (calculated by subtracting age at first major depressive or manic mood episode from the participants current age in years) was significantly longer in the BP+childhood ADHD group when compared to the BP-only group. The average age of BP onset, which was based on age at first mood episode (manic or depressive), was significantly younger in the BP+childhood ADHD group compared to the BP-only group. Similarly, the average age of depression onset was significantly younger in the BP+childhood ADHD group compared to the BP-only group. Participants in the BP+childhood ADHD group were also more likely than those in the BP-only group to have

Table 7: Medication consumed by the ADHD-only, BP-only, BP+childhood ADHD, and control groups in the week preceding the neuropsychological assessment

	ADHD-only (n = 27)		BP-only (n = 66)		BP+childhood ADHD (n = 18)		Control (n = 26)		χ^2	df	p
	n	%	n	%	n	%	n	%			
Any antipsychotic	2	7.4	27	40.9	7	38.9	0	0	26.17	3, 137	<.001
Atypical	1	3.7	26	39.4	7	38.9	0	0	-	-	-
Typical	1	3.7	1	1.5	0	0	0	0	-	-	-
Any mood stabilizer	1	3.7	45	68.2	9	50	0	0	54.68	3, 137	<.001
Lithium	1	3.7	22	33.3	1	5.6	0	0	-	-	-
Sodium Valproate	0	0	19	28.8	8	44.4	0	0	-	-	-
Carbamazepine	0	0	0	0	0	0	0	0	-	-	-
Any antidepressant	4	14.8	34	68.2	10	55.6	0	0	30.08	3, 137	<.001
SSRI	3	11.1	28	42.4	7	38.9	0	0	-	-	-
SNRI	1	3.7	8	12.1	2	11.1	0	0	-	-	-
RIMA	0	0	2	3	0	0	0	0	-	-	-
Tricyclic	0	0	3	4.5	0	0	0	0	-	-	-
Benzodiazepines	0	0	3	4.6	2	11.1	0	0	5.01	3, 137	.17
Any stimulant	7	25.9	0	0	1	5.6	0	0	25.52	3, 137	<.001
Any other psychotropic	0	0	1	0	0	0	0	0	-	-	-
Psychotropic's of 2 or more classes	4	14.8	44	66.7	11	55.6	0	0	45.84	3, 137	<.001

Table 8: *Illness progression factors that may impact on cognitive functioning in the BP and BP+childhood ADHD groups*

	BP-Only (n = 66)		BP+Childhood ADHD (n = 18)		<i>t</i>	<i>Df</i>	<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>			
Average bipolar disorder duration (years)	9.92	6.04	13.17	6.36	2.00	82	.049
Average age of bipolar disorder onset	15.76	5.14	12.11	4.07	2.78	82	.007
Average age of depression onset	15.71	4.65	12.89	4.55	2.29	81	.025
Average age of mania onset	21.38	5.56	18.15	6.59	1.75	53	.086
Average number of hospitalisations	1.56	4.19	.83	1.38	.72	82	.47
	<i>N</i>	<i>%</i>	<i>N</i>	<i>%</i>	χ^2	<i>Df</i>	<i>p</i>
Ten or more manic episodes in BPI	7	16.6	7	53.8	7.23	1, 55	.007
Ten or more depressive episodes	33	50.8	9	50.0	.003	1, 83	.95

experienced at least 10 manic episodes. The two BP groups did not differ significantly in terms of mania onset or having had experienced 10 or more depressive episodes.

Summary of Sample Demographics and the Presence of Variables Known to Impact on Cognitive Functioning.

The ADHD-only, BP-only, BP+childhood ADHD, and control groups differed significantly on 15 variables known to have some impact on neuropsychological functioning: sex distribution, premorbid IQ, the presence of cigarette use, depression and mania severity, the presence of a current anxiety disorder, the presence of a lifetime alcohol or substance use disorder, the presence of past psychotic symptoms, the presence of significant learning difficulties during childhood, the presence of abuse during childhood, the presence of moodstabilizers, the presence of antidepressants, the presence of stimulant medication, and the presence of two or more drug classes. The two bipolar disorder groups (BP-only and BP+childhood ADHD) differed significantly in terms of four illness progression features: age of onset of bipolar disorder and depression, illness duration, and number of manic episodes.

A Comparison of Psychomotor Speed, Nonverbal Memory, Verbal Declarative

Memory, Attention, and Executive Functioning in the ADHD-Only, BP-Only, BP+Childhood ADHD and Control Groups

Psychomotor speed. For information pertaining to basic psychomotor speed performance in the BP-only, ADHD-only, BP+childhood ADHD, and control groups, refer to Table 9. On a measure of psychomotor speed (CANTAB Motor Screening), the ADHD-only group demonstrated significantly faster response latencies than the BP-only group. The effect size was large. This effect was no longer significant after controlling for the severity of depression symptomatology (MADRS) or the presence of significant childhood learning

Table 9: Simple psychomotor speed performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.

Measure	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n = 18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	Df	P		
Motor Screening (mean correct latency, ms)	778.2	132.6	929.8	219	898.7	214.7	814.8	186.6	10.76	3, 130	< .001 ^{a b}	ADHD < BP-only (.84) < BP+childhood ADHD (.66) < Control (.23)	BP-only > Control (.57)
												BP+childhood ADHD > Control (.42) < BP-only (.14)	

^a Not significant after MADRS scores; ^b Not significant after covarying the presence of childhood learning difficulties

difficulties. It is noteworthy that the groups did not differ on an attention measure that heavily implicates psychomotor speed (Trail Making Test-Part A) (see below).

Nonverbal memory. A significant multivariate effect for group existed across the five nonverbal memory outcome measures (Wilks' Lambda = .67, $F(15, 348.23) = 3.57, p < .001$). This effect remained significant after controlling for all of the covariates. For specific information pertaining to nonverbal memory performance in the BP-only, ADHD-only, BP+childhood ADHD, and control groups, refer to Table 10.

The ADHD-only group made more errors across delays on the Delayed Matching to Sample (DMS) task relative to the BP, BP+childhood ADHD, and control groups. The effect sizes were large when the ADHD-only group was compared to the BP-only and control groups and medium when the ADHD-only group was compared to the BP+childhood ADHD group. On the Spatial Recognition Memory (SRM) task, the ADHD-only and BP-only groups each had a lower average percentage of correct responses when compared to the control group. Large effect sizes were present. The BP-only group was also shown to be slower than controls on the SRM response latency condition. The effect size for this latter difference was medium. This latter effect however was no longer present after controlling for the severity of depression symptomatology. On the Spatial Span (SS) task, the ADHD-only and BP-only groups each had a significantly lower mean span length compared to the control group. Large effect sizes were present. Nevertheless, group differences for this measure no longer remained significant after covarying depressive symptoms or the presence of significant childhood learning difficulties.

Verbal declarative memory. A significant multivariate effect for group existed across the 5 verbal memory outcome measures (Wilks' Lambda = .73, $F(15, 350.99) = 2.81, p < .001$). This effect remained significant after controlling for all of the covariates. For

Table 10: *Nonverbal memory performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.*

Measure	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n = 18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
Delayed Matching to Sample (DMS) (0 to 100% correct across three delays)	72.56	20.34	87.59	8.11	84.26	14.18	89.20	8.35	10.76	3, 130	< .001	ADHD	< Control (1.07) < BP-only (.97) < BP+childhood ADHD (.67)
												BP-only	< Control (.20)
												BP+childhood ADHD	< Control (.42) < BP-only (.29)
												ADHD	> BP+childhood ADHD (.26) < BP-only (.23) > Control (.09)
DMS (mean correct latency across all delays, ms)	3573.48	875.92	3822.29	1223.90	3338.28	947.50	3499.53	762.87	1.32	3, 130	.27	BP-only	< Control (.32)
												BP+childhood ADHD	< BP-only (.44) < Control (.19)

^a Not significant after MADRS scores; ^b Not significant after covarying the presence of childhood learning difficulties.

Note. Table 10 continues on the following two pages.

Table 10 continued: *Nonverbal memory performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.*

Measure	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n = 18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
Spatial Recognition Memory (SRM) (0 to 100% correct)	78.08	13.57	82.54	10.79	81.94	11.26	89.80	6.84	5.14	3, 130	.002	ADHD	< Control (1.09) < BP-only (.37) < BP+Childhood ADHD (.31)
												BP-only	< Control (.80)
												BP+childhood ADHD	< Control (.84) < BP-only (.05)
												ADHD	> Control (.85) > BP+Childhood ADHD (.35) > BP-only (.03)
SRM (mean correct latency, ms)	2543.13	650.25	2522.10	698.98	2318.06	647.91	2089.72	390.70	3.28	3, 130	.023 ^{a b}	BP-only	> Control (.76)
												BP+childhood ADHD	> Control (.43) < BP-only (.30)

^a Not significant after MADRS scores; ^b Not significant after covarying the presence of childhood learning difficulties

Note. Table 10 continues on the following page.

Table 10 continued: *Nonverbal memory performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.*

Measure	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n = 18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
Spatial Span (span length, 0 to 9)	5.81	1.70	6.09	1.53	6.22	1.67	7.20	1.16	4.22	3, 130	.007 ^{a b}	ADHD	< Control (.96) < BP+Childhood ADHD (.24) < BP-only (.17)
												BP-only	< Control (.82)
												BP+childhood ADHD	< Control (.68) > BP-only (.08)

^a Not significant after MADRS scores; ^b Not significant after covarying the presence of childhood learning difficulties

specific information pertaining to verbal declarative memory performance in the BP-only, ADHD-only, BP+childhood ADHD, and control groups, refer to Table 11. On a test that measured the short-term storage of numbers (Digit Span Forwards), the ADHD-only group had a significantly lower mean score relative to the BP-only group. The effect size was large. Nevertheless, this effect no longer remained significant after controlling for estimated IQ. On the Rey Auditory Verbal Learning Test (RAVLT), the ADHD-only group had a significantly lower mean score on the immediate recall condition compared to the BP-only and control groups. The effect size was large when the ADHD-only group was compared to the control group, and medium when the ADHD-only group was compared to the BP-only group. On the delayed condition of the RAVLT, the ADHD-only group had a lower mean score relative to the controls. The effect size was large. On the verbal learning condition of the RAVLT (the sum of scores for List A for trials one to five), the ADHD-only group had a significantly lower mean total score compared to the BP-only and control groups. Large effect sizes were present. On the verbal recognition component of the RAVLT, the percentage of List A items correctly recognised was significantly lower in the ADHD-only group compared to the control group. A medium effect size was present. This group effect no longer remained after controlling for sex.

Attention. A significant multivariate effect for group existed across the four attention outcome measures (Wilks' Lambda = .77, $F(12, 325.72) = 2.76$, $p = .001$). This effect remained significant after controlling for all of the covariates. For specific information pertaining to performance on sustained attention measures in the BP-only, ADHD-only, BP+childhood ADHD, and control groups, refer to Table 12.

Target sensitivity scores on the Rapid Visual Information Processing (RVIP) were significantly lower in the ADHD-only group compared to the control group with a medium effect size being present. On the RVIP test, the ADHD-only and BP-only groups both

Table 11: *Verbal declarative memory and learning performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.*

Measure	ADHD-only (n = 27)		BP-only (n =66)		BP+childhood ADHD (n = 18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
Rey Auditory Verbal Learning Test (RAVLT) (list A – trial 1, 0 to 15 correct)	6.67	1.75	7.86	1.99	7.28	1.99	8.50	1.84	4.55	3, 131	.005	ADHD < Control (1.02) < BP-only (.64) < BP+Childhood ADHD (.33)	
												BP-only < Control (.33)	
												BP+childhood ADHD < Control (.64) < BP-only (.29)	
RAVLT (list A – trials 1 to 5, 0 to 75 correct)	48.89	9.01	57.11	7.41	51.72	8.57	57.38	7.34	8.72	3, 131	< .001	ADHD < Control (1.03) < BP-only (1.00) < BP+Childhood ADHD (.32)	
												BP-only < Control (.04)	
												BP+childhood ADHD < Control (.71) < BP-only (.67)	

^a Not significant after covarying sex; ^b Not significant after covarying IQ based on the NART

Note. Table 11 continues on the following two pages.

Table 11 continued: *Verbal declarative memory and learning performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.*

Measure	ADHD-only (n = 27)		BP-only (n =66)		BP+childhood ADHD (n = 18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
RAVLT (list A – trial 7, 0 to 15 correct)	9.67	3.39	11.36	2.86	10.61	2.66	12.31	2.31	4.18	3, 131	.007	ADHD	< Control (.91) < BP-only (.54) < BP+Childhood ADHD (.31)
												BP-only	< Control (.37)
												BP+childhood ADHD	< Control (.68) < BP-only (.27)
RAVLT (list A – recognition, 0 to 100% correct)	83.96	14.47	90.73	11.20	90.37	11.48	93.08	9.69	3.08	3, 131	.030^a	ADHD	< Control (.74) < BP-only (.52) < BP+Childhood ADHD (.49)
												BP-only	< Control (.22)
												BP+childhood ADHD	< Control (.26) < BP-only (.03)

^a Not significant after covarying sex; ^b Not significant after covarying IQ based on the NART
Note. Table 11 continues on the following page.

Table 11 continued: *Verbal declarative memory and learning performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.*

Measure	ADHD-only (n = 27)		BP-only (n =66)		BP+childhood ADHD (n = 18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
Digit Span (forwards span, 0 to 9)	6.00	1.36	7.05	1.19	6.56	1.04	6.85	1.29	4.82	3, 131	.003 ^b	ADHD	< BP-only (.82)
													< Control (.64)
													< BP+Childhood ADHD (.46)
												BP-only	> Control (.16)
												BP+childhood ADHD	< BP-only (.44)
													< Control (.25)

^a Not significant after covarying sex; ^b Not significant after covarying IQ based on the NART

Table 12: Sustained attention performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.

Measure	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n =18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
RVIP (total omission errors)	11.93	5.07	10.86	5.56	9.31	4.30	7.46	4.70	3.74	3, 126	.013	ADHD > Control (.91) > BP+childhood ADHD (.56) > BP-only (.20)	
												BP-only > Control (.66)	
												BP+childhood ADHD > Control (.41) < BP-only (.31)	
RVIP (target sensitivity, 0.00 to 1.00)	.88	.05	.90	.05	.91	.04	.93	.05	3.85	3, 126	.011	ADHD < Control (1.00) < BP+childhood ADHD (.66) < BP-only (.40)	
												BP-only < Control (.60)	
												BP+childhood ADHD > Control (.44) < BP-only (.22)	

Note. Table 12 continues on the following page.

Table 12 continued: *Sustained attention performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.*

Measure	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n =18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
Rapid Visual Information Processing (RVIP) (mean correct latency, ms)	447.27	122.45	471.26	128.63	422.48	90.85	403.16	120.51	2.08	3, 126	.11	ADHD	> Control (.36)
													> BP+childhood ADHD (.23)
													< BP-only (.19)
Trail Making Test (part A, time in seconds)	25.48	8.01	29.38	10.26	26.38	8.31	24.12	5.66	2.60	3, 126	.055	BP-only	> Control (.55)
												BP+childhood ADHD	< BP-only (.44)
													> Control (.18)
												ADHD	< BP-only (.42)
													> Control (.20)
													< BP+childhood ADHD (.11)
												BP-only	> Control (.63)
												BP+childhood ADHD	> Control (.32)
													< BP-only (.32)

demonstrated a significantly higher rate of omission errors relative to the control group. Effect sizes were in the large and medium ranges, respectively. No effect for group was evident for the RVIP test response latency condition or the Trail Making Test Part A.

Executive functioning. A non-significant multivariate effect for group existed for the six primary executive functioning outcome measures: CANTAB Spatial Working Memory (SWM) test (strategy score and number of between search errors), Trail Making Test (part B, seconds), Digit Span (backwards span) test, Verbal Fluency Test (total score), and commission errors on the Rapid Visual Information Processing (RVIP) Test (Wilks' Lambda = .90, $F(15, 342.71) = 0.890$, $p = .58$). For specific information pertaining to performance on these measures among the BP-only, ADHD-only, BP+childhood ADHD, and control groups, refer to Table 13.

It should be noted that the results for two BP+childhood ADHD participants were removed prior to conducting the aforementioned analysis due to unusually high rates of commission errors on the RVIP test. The number of RVIP test commission errors committed by these two participants (21 and 36) was significantly higher than what was expected given the BP+childhood ADHD groups mean score and standard deviation values ($M = 4.39$, $SD = 9.33$). Hence, it is plausible that they were responding randomly or did not understand all of the instructions for the RVIP test.

Summary of Neuropsychological Performance.

The ADHD-only group did not differ from the BP+childhood ADHD group on every neuropsychological measure except for one; a visual memory outcome measure (DMS percent correct across delays) where there was a moderate effect.

Table 13: *Executive functioning performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.*

Measure	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n =18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
Spatial Working Memory (SWM) (total between errors)	22.58	15.58	18.76	15.54	17	18.21	12.13	10.18	2.10	3, 124	.10	ADHD	> Control (.79)
													> BP+childhood ADHD (.33)
													> BP-only (.25)
												BP-only	> Control (.50)
SWM (strategy score, 8 to 56)	31.69	4.82	30.63	5.86	28.60	6.77	28.46	5.61	1.84	3, 124	.14	BP+childhood ADHD	> Control (.33)
													< BP-only (.10)
												ADHD	> Control (.62)
													> BP+childhood ADHD (.53)
												BP-only	> Control (.38)
												BP+childhood ADHD	< BP-only (.32)
													> Control (.02)

Note. Table 13 continues on the following two pages.

Table 13 continued: *Executive functioning performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.*

Measure	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n =18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
Controlled Oral Word Association Test (total score)	37.69	14.08	41.67	10.89	43.53	12.37	42.08	10.22	1.07	3, 124	.37	ADHD	< BP+childhood ADHD (.44) < Control (.36) < BP-only (.32)
												BP-only	< Control (.04)
												BP+childhood ADHD	> BP-only (.16) > Control (.13)
Digit Span (backwards span, 0 to 9)	4.69	1.44	5.13	1.27	5.40	1.30	5.63	1.35	2.26	3, 124	.085	ADHD	< Control (.67) < BP+childhood ADHD (.52) < BP-only (.32)
												BP-only	< Control (.38)
												BP+childhood ADHD	> BP-only (.21) < Control (.17)

Note. Table 13 continues on the following page.

Table 13 continued: *Executive functioning performance in the ADHD-only, BP-only, BP+childhood ADHD, and control groups.*

Measure	ADHD-only (n =27)		BP-only (n =66)		BP+childhood ADHD (n =18)		Control (n =26)		ANOVA			Contrasts & Effect Sizes (d)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p		
Trail Making Test (part B, time in seconds)	72.88	24.21	68.68	29.03	59.80	25.91	56.67	17.99	2.15	3, 124	.098	ADHD	> Control (.76)
													> BP+childhood ADHD (.52)
													> BP-only (.16)
												BP-only	> Control (.50)
Rapid Visual Information Processing (total commission errors)	2.12	2.46	.86	1.12	1.25	1.54	1.47	2.03	3.63	3, 124	.015	BP+childhood ADHD	< BP-only (.32)
													> Control (.14)
												ADHD	< BP-only (.66)
													> BP+childhood ADHD (.42)
													> Control (.29)
												BP-only	> Control (.37)
												BP+childhood ADHD	< BP-only (.29)
													> Control (.12)

The ADHD-only group was largely impaired relative to the BP-only group on one measure of verbal memory (RAVLT verbal learning) and on one measure of visual memory (DMS percent correct across delays). On one additional measure of verbal memory (RAVLT immediate recall), and a measure of attention (RVIP commission errors), the ADHD-only group was shown to be moderately impaired relative to the BP group.

Compared to controls, the ADHD-only group was largely impaired on two visual memory measures (DMS percent correct across delays; SRM percent correct; SS span length), three verbal memory measures (RAVLT immediate recall; RAVLT delayed recall; RAVLT verbal learning), and one attention measure (RVIP omission error).

The BP-only group did not perform significantly worse than the BP+childhood ADHD group, or the ADHD-only group (except for the RAVLT verbal learning and immediate recall conditions, and the DMS accuracy measure - see above) on any of the neuropsychological measures. Compared to the control group, participants in the BP-only group were largely impaired on one measure of visual memory (SRM percent correct). The BP-only group was moderately impaired relative to controls on one measure of attention (RVIP omission errors).

CHAPTER 4: Discussion

This study aimed to clarify whether the neurocognitive impairments often detected in adult BP are partially the result of lifetime ADHD. A group with confirmed diagnoses of adult ADHD (ADHD-only group) was shown to perform significantly worse than a BP without past lifetime ADHD group (BP-only) and controls on measures of short-term verbal memory and verbal learning. Similarly, the ADHD-only group performed worse than controls on a measure of long-term verbal memory. On a measure of short-term visual-object memory, the ADHD-only group was impaired relative to individuals who had BP with childhood ADHD (BP+childhood ADHD), a BP-only group, and controls. Finally, the ADHD-only and BP-only groups both performed worse than a control group on a measure of short-term spatial memory and on a test of sustained attention. Such findings were broadly inconsistent with the present investigation's core hypothesis that a BP+childhood ADHD group and an ADHD-only group would be similarly yet greatly impaired relative to a BP-only group and controls across measures of verbal declarative memory, nonverbal memory, sustained attention, and executive functioning. As predicted however, the four groups did perform similarly on a measure of simple psychomotor speed after controlling for depression symptomatology and learning difficulties.

As detailed in the Implications of Research and Future Directions sub-section, a major strength of this study is that it detected group effects on cognitive measures whilst simultaneously addressing various limitations associated with previous research. Specifically, the results of many similar investigations have poorer external validity due to the use of stringent inclusion criteria. Other limitations of previous research include the absence of adult samples, and the absence of four comparison groups: BP-only, ADHD-only, BP+lifetime ADHD, and control groups.

Similarly, the accuracy of findings in many other studies is often questionable because they failed to control for clinical and non-clinical variables known to influence particular cognitive functions: the presence of past psychosis, past child abuse, nicotine/cafeine use, medication, and IQ. Despite the aforementioned limitations of previous research, it is helpful that most studies with adults have employed the SCID-I to assess for Axis I conditions and have used mood rating scales that are either identical or qualitatively similar to those used in the present investigation. It is also useful that most studies have included broadly similar inclusion criteria for the BP samples and have controlled for certain covariates known to impact on a wide range of cognitive functions such as sex, and age.

In instances where the methodology employed in the current investigation is weak or is of a poor quality relative to that used in similar studies, details are provided in the Limitations sub-section. In brief, such limitations involve the quality of assessment measures, the validity of various covariate indicators, the absence of other significant covariate measures, and the relevance of the sample source for the two BP groups. Some of the differences in methodology that exist between the present investigation and the five other neuropsychological studies which have compared BP with and without lifetime ADHD groups are not related to design quality (Dickstein et al., 2004; Mattis et al., 2006; McClure et al., 2005; Pavuluri et al., 2006; Rucklidge, 2006). Nonetheless, the differences are of consequence as they help to place the current study's results within a broader context. Hence the potential impact of test type and age will be considered throughout the Findings section.

Findings

The impact of lifetime ADHD on verbal declarative memory in BP. In the present study, the BP+childhood ADHD group performed similarly to the BP-only, ADHD, and control groups on all five measures of verbal declarative memory. Such tests implicate short-

term (span length for Digit Span Forwards or DSF; trial one of the Rey Auditory Verbal Learning Test or RAVLT) and long-term (trial eight of the RAVLT) memory, learning ability (trials one to five of the RAVLT), and recognition memory (recognition condition of the RAVLT). In fact, it was only a group with confirmed diagnoses of adult ADHD (ADHD group) that demonstrated significant difficulties in the verbal declarative memory domain relative to a control group. Specifically, the ADHD group was impaired relative to controls and the BP-only group on a word list paradigm's short-term memory and learning conditions. Also, the ADHD group was impaired relative to controls on the long-term memory condition of the word list paradigm. It is surprising that the BP+childhood ADHD group was not more impaired than the BP-only group on measures of verbal declarative memory because in addition to experiencing lifetime ADHD symptoms, it exhibited significantly higher rates of clinical features known to impact on this cognitive domain in BP: a lower age of BP onset (Bora et al., 2009), a higher number of manic episodes (Cavanagh et al., 2002; Martinez-Aran et al., 2004; Deckersbach et al., 2004), and higher rates of child abuse (Savitz et al., 2008).

A comparison is now made between the present study's results and those of the four other studies (Mattis et al., 2006; McClure et al., 2005; Pavuluri et al., 2006; Rucklidge, 2006) which compared BP with and without ADHD groups on measures of verbal declarative memory. Like the present study, Rucklidge (2006), McClure et al. (2005), Pavuluri et al. (2006), and Mattis et al. (2011) failed to detect significant differences between BP with and without ADHD groups on measures of declarative verbal memory. Unlike the present study however, two of these studies found that ADHD may still contribute to declarative memory impairment in BP as only the BP with comorbid ADHD groups were impaired relative to controls on list learning (including short-term memory, verbal learning, verbal recognition memory, and long-term memory) (McClure et al., 2005; Rucklidge, 2006) and short-term story recall (McClure et al., 2005; Rucklidge, 2006) paradigms. It is unclear whether this

pattern also held for the Pavuluri et al. (2006) study as a group which consisted of both BP- with and without comorbid ADHD performed worse than controls as a whole on a composite measure of verbal declarative memory. Unfortunately, the Mattis et al. (2011) study failed to include a control group though noted that both BP groups performed similarly to an ADHD-only group.

It is significant that the verbal declarative memory measures employed in the present investigation differed from those employed in the McClure et al. (2005) and Rucklidge (2006) studies. Whereas McClure et al. (2005) found that the presence of ADHD contributed to poorer performances on the CVLT, Pavuluri et al (2006) and Mattis et al. (2011) did not. The present study failed to replicate McClure et al. (2005) pattern of results for the BP+childhood ADHD group using the RAVLT, a variant of this task. Unlike the CVLT, the RAVLT consists of a semantically unrelated word list, and is thus less sensitive to executive dysfunction (Golden, Espe-Pfeifer, & Wachsler-Felder, 2000). To date, there are no other studies that have applied the RAVLT to individuals who have BP with lifetime ADHD. Although the presence of ADHD contributed to poorer performances on the short-term story recall conditions of the WRAML and the TOMAL in the McClure et al. (2005) and Rucklidge (2006) studies, it is significant that these tests involve story recall, a skill which is “distinctly independent” from list memory, and involves the provision of more organisation as well as meaning (Golden et al., 2000, p. 194). Indeed, research with adults suggests that story recall is relatively preserved in adult ADHD with a meta-analytic study detecting small to minimal effects (Hervey et al., 2004, p. 194).

It is important to consider the role of age when interpreting the aforementioned results. It is plausible that some of the studies neglected to detect impairment on word learning paradigms because they consisted of child samples (Mattis et al., 2006; McClure et al., 2005; Pavuluri et al., 2006; Rucklidge, 2006). Indeed, there is evidence that the use of verbal encoding

strategies which enhances performance on word learning tasks in particular (e.g. the use of semantic clustering), develops during adolescence (not childhood) (Gathercole, 1998). Child controls and child ADHD samples may thus have both been similarly competent at utilising forms of memory that require minimal levels of conscious control. Indeed, research suggests that it is the poor use of encoding strategies that places ADHD adolescents and adults at a disadvantage on list learning paradigms (August, 1987; Egeland et al., 2010; Pollak et al., 2008). Hence, it may be this latter deficit that accounts for the poor performance of the ADHD-only group on the RAVLT. Had the BP+childhood ADHD group demonstrated current ADHD, it too may have been similarly impaired.

To help place the results for the BP+childhood ADHD group in context, attention will now be given to the results from other studies of adult BP which employed similar measures of verbal declarative memory, but failed to control for the effects of lifetime ADHD. In general terms, it is surprising that the BP+childhood ADHD (or BP-only) group performed similarly to controls on measures of verbal declarative memory as meta-analytic studies of adults in euthymic phase BP have consistently detected medium to large effects for this domain using word learning paradigms (except for measures of verbal recognition memory, where effects have tended to be small) (Arts et al., 2008; Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006; Torres et al., 2007). The BP+childhood ADHD group's performance on a number span test was less surprising as meta-analytic studies have only detected small effects for such tests among adults who are experiencing euthymic phase BP (Arts et al., 2008; Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006).

Compared to the other studies reviewed (except for Thompson et al., 2005) that did detect impairment among euthymic phase BP samples using the RAVLT, the BP samples employed in the present investigation were markedly younger (Bora et al., 2007; Ferrier et al., 1999;

Goswami et al., 2006; Kaya, Aydemir, & Selcuki, 2007; Krabbendam et al., 2000; Schouws et al., 2007; Thompson et al., 2005; Varga et al., 2006). This is significant given that the number of manic episodes, which will increase over time (Cavanagh et al., 2002; Deckersbach et al., 2004; Martinez-Aran et al., 2004) has been associated with poor declarative verbal memory in BP. Hence, it is plausible that factors other than ADHD, including age may have contributed to RAVLT impairment in these other studies.

Findings from neurobiological studies give some support to the notion that current diagnoses of ADHD may contribute to poor performances on measures of short-term verbal memory and verbal learning in BP. Using the RAVLT, neuroimaging studies have found greater activation during the successful encoding of subsequently recalled words in the temporal lobes and the cerebellum during the short-term recall and verbal learning trials (Balthazar et al., 2010; Brassen et al., 2006). Neuroimaging studies have detected Temporal lobe abnormalities in ADHD (Castellanos et al., 2002; Sowell et al., 2003). Indeed, a number of neuroimaging studies have also detected reductions in cerebellum volume in children/adolescents who have ADHD (Berquin et al., 1998; Bussing, Grudnik, Mason, Wasiak, & Leonard, 2002; Castellanos et al., 1996; Castellanos et al., 2001; Hill et al., 2003).

The impact of lifetime ADHD on nonverbal memory in BP. In the present study, the BP+childhood ADHD group performed similarly to the BP-only, and control groups on all five nonverbal memory outcome measures: including two short-term visual object memory conditions (percentage correct across three delays on the CANTAB Delayed Matching to Sample or DMS; mean correct latency across all delays on the DMS), and three short-term spatial memory conditions (percentage correct for the CANTAB Spatial Recognition Memory or SRM; mean correct latency for the SRM; span length for the Spatial Span or SS). Surprisingly, the BP-only group performed worse than controls on a measure of short-term spatial memory (percentage correct for the SRM). The ADHD-only group also

performed worse than the controls on this measure. In addition, the ADHD-only group performed significantly worse than the other three groups on a measure of short-term visual object memory (percentage correct across delays). It is surprising that the BP+childhood ADHD group was not more impaired than the BP-only group on measures of nonverbal memory as in addition to experiencing a history of ADHD symptoms, it exhibited significantly higher rates of clinical features known to impact on this cognitive domain in BP: child abuse (Savitz et al., 2008) and manic episodes (Deckersbach et al., 2004). Nevertheless, some other studies have failed to detect an association between manic episodes and poor nonverbal memory (MacQueen et al., 2001; Rubinsztein et al., 2000).

A comparison is now made between the present investigations results and those of the two other studies (Dickstein et al., 2004; Rucklidge, 2006) which compared BP with and without ADHD groups on measures of nonverbal memory. Like the present study, these two additional studies also failed to detect significant differences between the two BP groups on such tasks. In contrast to what was hypothesised however, the present study's results suggest that BP and ADHD may each be independently associated with poor short-term spatial memory. More research is required however as Rucklidge (2006) failed to detect impairment on a measure of short-term spatial memory in BP-only or ADHD-only groups relative to controls. It is unclear whether Dickstein et al. (2004) would have found similar results to Rucklidge (2006) as they failed to compare the two BP groups to a control group, or an ADHD-only group (though they did detect impairment on a measure of short-term spatial memory in the BP sample as a whole relative to controls). Given that in the present study, it was only an ADHD-only group that demonstrated impaired short-term visual-object memory relative to controls, it is plausible that ADHD, if shown to persist into adulthood, may underlie such deficits in BP. Again, further research is required however as Rucklidge (2006)

failed to detect impairment on a measure of short-term visual-object memory in BP-only or ADHD-only groups relative to controls.

It is noteworthy that the nonverbal memory measures employed in the present investigation differed in some instances from those employed in the Dickstein et al. (2004) and Rucklidge (2006) studies. With regard to visual-object memory, Dickstein et al. (2004) employed the CANTAB Pattern Recognition Memory test which unlike the DMS is designed to make it difficult for individuals to generate verbal encoding. Indeed, it has seldom been associated with differences between controls and adult (McLean et al., 2004) or adolescent (Kempton et al., 1999) ADHD samples. It is noteworthy that the DMS implicates the use of verbal encoding strategies as this is a skill area which is frequently impaired in ADHD (August, 1987; Egeland, Johansen & Ueland, 2010; Pollak et al., 2008). Moreover, Rucklidge (2006) used the WRAML Picture Memory subtest which uses a testing format significantly different to the test of visual-object memory employed in the present study. Unlike the DMS, it requires participants to remember meaningful pictures (e.g. a scene where people sat around a table during a meeting) and not abstract patterns. Indeed, other studies have also failed to detect impaired performance among ADHD participants on this measure (Mealer, Morgan, & Luscomb, 1996). With regard to short-term spatial memory, Rucklidge (2006) drew on the WRAML Finger Windows test instead of the SS or SRM tasks. As explained in a previous section, the psychometric properties of the WRAML Finger Windows subtest are questionable as it correlates more with measures of attention than with nonverbal memory (Haut, Haut, & Franzen, 1992). Regardless, it is significant that Dickstein et al. (2004) also failed to detect impairment in a BP group after controlling for lifetime ADHD on the two measures of short-term spatial memory that were employed in this study. In light of some of the methodological differences between the present investigation and the Dickstein et al. (2004) study, further research is needed.

In interpreting the aforementioned results for the nonverbal memory domain, consideration must be given to the role of age. Although the latter studies involve child/adolescent samples, the results suggest that nonverbal memory abilities may be rather similar (regardless of whether impairment is present or not) across the age range in both ADHD and BP. This is also supported by studies that did not control for lifetime ADHD (see below). Nevertheless, it is noteworthy that short-term visual-picture memory was only impaired in the current study's ADHD-only group. Like the RAVLT, the DMS test benefits from the use of verbal encoding strategies which develop during adolescence (Gathercole, 1998) and as discussed earlier, such strategies are more likely to be impaired in ADHD adolescents and adults (August, 1987; Egeland et al., 2010; Pollak et al., 2008). Hence, it may be this latter deficit that accounts for the poor performance of the ADHD-only group on the DMS test. Had the BP+childhood ADHD group demonstrated current ADHD, it too may have been similarly impaired.

To help place the results for the BP+childhood ADHD group in context, attention will now be given to the results from other studies of adult BP which employed identical measures of nonverbal memory, but failed to control for the effects of lifetime ADHD. In general terms, it is surprising that the BP-only group but not the BP+childhood ADHD group was impaired relative to controls on measures of nonverbal memory. Impairment in the BP-only group was consistent with the results of most other study's (Badcock et al., 2005; Murphy et al., 1999; Roiser et al., 2009; Rubinsztein et al., 2006; Sweeney et al., 2000; Thompson et al., 2005).

Despite the aforementioned differences in methodology between the present investigation and those other studies of adult BP that employed the SRM, SS, and DMS, it seems unlikely that the presence of lifetime ADHD can fully account for the full spectrum of nonverbal memory impairments in BP. Given that the BP-only and ADHD-only groups were similarly impaired relative to controls on a measure of short-term spatial memory which employs a binary

choice recognition paradigm (the SRM test), it is plausible that both disorders share some overlapping neural pathology. It was not particularly surprising that the ADHD-only group was impaired on the SRM test relative to controls as similar results have been found in controlled studies of adolescent ADHD (Kempton et al., 1999; Rhodes et al., 2005; Vance et al., 2003). Research with neurosurgical patients and neuroimaging studies demonstrates that the spatial memory test in question implicates the dorsolateral prefrontal cortex (DLPFC) (Goldberg, Berman, Randolph, Gold, & Weinberger, 1996; McCarthy et al., 1994; Owen et al., 1995; Owen et al., 1996). In a review by Seidman, Valera, & Makris (2005), nine studies of ADHD identified smaller prefrontal volumes in areas corresponding to the DLPFC. In a recent meta-analytic study, decreased DLPFC volumes were also reported for BP (Houenou et al., 2011).

Like the ADHD-only group, individuals in the BP+childhood ADHD group may have also demonstrated poorer short-term visual object memory relative to the BP-only and control groups if their ADHD diagnoses had been demonstrated to persist into adulthood. While no other study appears to have compared adult ADHD and control groups on the DMS test, three controlled studies did detect markedly poorer accuracy scores on this instrument in adolescents with ADHD (Kempton et al., 1999; Rhodes et al., 2005; Vance et al., 2003). It is of note that the DMS test implicates target detection skills more so than many other non-verbal memory paradigms as individuals with ADHD have been shown to demonstrate impairment in this area (Bush et al., 2002). As mentioned above, it also implicates the use of encoding strategies known to often be impaired in ADHD. In individuals with confirmed diagnoses of ADHD, pre-existing difficulties with sustaining attention may have been exploited by the design of the DMS test, which in turn may have contributed to low accuracy scores. The design of the DMS task may have amplified such difficulties as it includes a

lengthy administration time (i.e. approximately 15 to 20 minutes) and a particularly repetitive format (two, twenty item blocks with a short break in between).

Findings from neurobiological studies give some support to the notion that a current comorbid diagnosis of ADHD may partially account for poor performances on measures of visual object memory in BP. Research with neurosurgical patients and neuroimaging studies demonstrates that the test of visual object memory which was used in this study implicates brain regions such as the temporal lobes (Monk et al., 2002; Owen et al., 1995; Picchioni et al., 2007) and the anterior cingulate cortex (Pessoa et al., 2002; Picchioni et al., 2007). This is of note, given that some neuroimaging research of ADHD has described reduced white and grey matter volumes in temporal (Castellanos et al., 2002; Sowell et al., 2003) and anterior cingulate cortex regions (Bush et al., 1999; Rubia et al., 1999; Seidman et al., 2006; Tamm et al., 2004; Tian et al., 2006). Also, it is significant that the visual object memory test employed in this study involves “large-scale neurocognitive networks” which implicate a raft of cognitive functions (Luciana & Nelson, 1998, p. 286). Indeed, there is some evidence that compared to BP, ADHD may be characterized by more widespread neurobiological dysfunction. In a neuroimaging study by Passarotti, Sweeney, and Pavuluri (2010), prefrontal dysfunction was more extensive in ADHD compared to BP during an inhibition task and was associated with more subcortical overactivity. Moreover, using diffusion tensor imaging, Pavuluri et al. (2009) detected more extensive cellular abnormalities across white matter tracts in child/adolescent BP compared to ADHD.

The impact of lifetime ADHD on attention in BP. In the present study, the BP+childhood ADHD group performed similarly to the BP-only, ADHD and control groups on all four sustained attention outcome measures: three of which pertained to the RVIP (a continuous performance test or CPT) (target sensitivity, omission errors, and response latencies), and one of which involved completion times for a measure with a strong motor

component (TMT-A). Whereas the BP-only and ADHD groups made significantly more RVIP omission errors than controls, the ADHD group also had lower RVIP target sensitivity scores compared to controls. It is surprising that the BP+childhood ADHD group was not more impaired than the BP-only group on measures of sustained attention as it demonstrated significantly higher rates of clinical features known to be associated with poor performance in this cognitive domain: a longer duration of illness (Bora et al., 2007; Clark et al., 2002), a higher frequency of manic episodes (Bora et al., 2007; Clark et al., 2002), and a younger average age of illness onset (Bora et al., 2009).

A comparison is now made between the present study's results and those of the three other studies (Mattis et al., 2011; Pavuluri et al., 2006; Rucklidge, 2006) which explicitly compared BP with and without lifetime ADHD groups on measures of sustained attention. Like the present investigation, two of these studies failed to detect significant differences between the two types of BP groups on measures of sustained attention which were presented through trail making (Rucklidge, 2006) or continuous performance (Mattis et al., 2011; Rucklidge, 2006) paradigms. Unlike the Mattis et al. (2011) and Rucklidge (2006) studies, the BP with lifetime ADHD group was not more impaired than an ADHD-only group and in the case of the Rucklidge (2006) study, a control group as well. Unlike the Rucklidge (2006) study, the present study detected impairment in the BP-only group on the CPT relative to controls. Given that Mattis et al. (2006) found that a BP-only group was impaired relative to an ADHD group on this measure, it is quite plausible that sustained attention difficulties in BP may occur independently of lifetime ADHD. Nevertheless, it is plausible that ADHD may still have an effect on attention in BP as Pavuluri et al. (2006) found that a BP with comorbid ADHD group was significantly impaired relative to a BP without lifetime ADHD group using a composite measure that averaged scores across two tests of sustained attention. In light of these variable results, it is clear that more research may be required.

It is noteworthy that the sustained attention measures employed in the present investigation differ from those employed in these three studies. In terms of continuous performance paradigms, Rucklidge (2006) and Mattis et al. (2006) employed the Connor's CPT rather than a more traditional CPT such as the RVIP test. Compared to the RVIP test, this instrument has a higher signal probability (that is, many signals are embedded among a few non-signal stimuli) and hence is less likely to be associated with omission errors (Hervey et al., 2004). Pavuluri et al. (2006) used the Penn CPT to measure sustained attention. Although it implicates working memory to a lesser degree than the RVIP, this is unlikely to be too significant as it has good convergent validity with such measures, including the Gordon Diagnostic CPT (Kurtz, Ragland, Bilker, Gur, & Gur, 2001). Although Rucklidge (2006) used Color Trails 1 instead of the TMT-A, both measures are very similar and have been shown to measure the same underlying constructs (Lee & Chan, 2000; Maj et al., 1993). With this regard, it is helpful that like the present investigation, Pavuluri et al. (2006) also used the TMT-A to help assess sustained attention.

In interpreting the aforementioned results for the nonverbal memory domain, consideration is given to the role of age. Although the latter studies involve child/adolescent samples, the results suggest that sustained attention as indexed by CPTs and the TMT-A may be rather similar (regardless of whether impairment is present or not) across the age range in both ADHD and BP. This is also supported by studies that did not control for lifetime ADHD (see below). Nevertheless, it may be inappropriate to draw comparisons between studies of children/adolescents and the present study as Color Trails 1 and the TMT-A have both been shown to be particularly vulnerable to age effects in healthy individuals (Lee & Chan, 2000; Maj et al., 1993).

To help place the results for the BP+childhood ADHD group in context, attention will now be given to the results from other studies of adult BP which employed similar measures of

sustained attention but may have failed to control for the effects of lifetime ADHD. In general terms, it is surprising that the BP-only group but not the BP+childhood ADHD group was impaired relative to controls in this cognitive domain. Impairment in the BP-only group on the RVIP test was consistent with the results of meta-analytic studies that have applied CPTs to adults in euthymic phase BP (Arts et al., 2009; Bora et al., 2009; Kurtz & Gerraty, 2009; Torres et al., 2007). Given that medium meta-analytic effects are often detected for BP adults using trail making paradigms, it is surprising that neither BP group was impaired on the TMT-A (Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006; Torres et al., 2007).

Given that the BP-only and ADHD groups were both impaired relative to controls on a CPT, it is likely that both disorders may share some overlapping neural pathology. The finding that an ADHD group demonstrated significantly higher rates of omission errors and lower target sensitivity scores on a CPT relative to controls was broadly consistent with the results of meta-analytic research (Boonstra et al., 2005; Hervey et al., 2004). A few neuroimaging studies have considered the performance of individuals with ADHD during tests of sustained attention. In a study by Cubillo et al. (2011), young adults who had ADHD showed dysfunctions in lateral fronto-striatal-parietal regions relative to controls during a CPT. In a study of children, ADHD was associated with reduced functional connectivity relative to controls between the inferior frontal cortex, basal ganglia, and parietal lobes, and between the cerebellum, parietal and striatal brain regions during a sustained attention task (Rubia et al., 2009). With regard to BP, regional activation decrements in the DLPFC have been shown to accompany sustained attention decrements in both bipolar and healthy individuals (Fleck et al., 2012).

The impact of lifetime ADHD on executive functioning and psychomotor speed in BP. As expected, the BP+childhood ADHD, BP-only, ADHD, and control groups

performed similarly across one measure of simple psychomotor speed (CANTAB Motor Screening or MS). Conversely, it was surprising that the BP+childhood ADHD, ADHD, BP-only, and control groups performed similarly across six executive functioning outcome measures which involve cognitive flexibility (completion times for Trail Making Test Part B or TMT-B), working memory (between errors and strategy scores on CANTAB Spatial Working Memory test or SWM; backwards span length for Digit Span or DSB), verbal fluency (total score on Controlled Oral Word Association Test or COWAT), and inhibition (commission errors on RVIP). It is surprising that the BP+childhood ADHD group was not more impaired than the BP-only group on measures of executive functioning as it exhibited significantly higher rates of lifetime manic episodes, a clinical feature known to be associated with poor performance in this cognitive domain (Van Gorp et al., 1998; Zubieta et al., 2001).

A comparison is now made between the present study's results and those of the four other studies (Dickstein et al., 2004; Mattis et al., 2011; Pavuluri et al., 2006; Rucklidge, 2006) which compared BP with and without ADHD groups on measures of executive functioning and simple psychomotor speed. Like the present study, such studies failed to detect significant differences between BP with and without ADHD groups on measures of inhibition (Dickstein et al., 2004; Mattis et al., 2011; Pavuluri et al., 2006; Rucklidge, 2006), cognitive flexibility (Rucklidge, 2006; Dickstein et al., 2006; Mattis et al., 2011), and working memory (Rucklidge, 2006; Dickstein et al., 2006). Nevertheless, unlike the present study, Rucklidge (2006) found that ADHD may contribute to executive dysfunction in BP as only the combined and ADHD groups were impaired relative to controls on a measure of inhibition. It is unclear whether Dickstein et al. (2004) and Mattis et al. (2004) would have found similar results to Rucklidge (2006) as they failed to compare the two BP groups to a control group. Unlike the present study, Pavuluri et al. (2006) found that a BP with comorbid ADHD group was significantly impaired relative to a BP without lifetime ADHD group using a composite

measure that averaged scores across four tests of executive function (including cognitive flexibility, and verbal fluency). Also, unlike the present study, Mattis et al. (2011) found that a BP with comorbid ADHD group was impaired on a measure of verbal fluency compared to a BP-only group. Only two other studies have compared BP with and without ADHD groups on measures of simple psychomotor speed (Dickstein et al., 2006; Pavuluri et al., 2006). Like the current study, no effects were detected between the two BP groups on such measures. In the Pavuluri et al. (2006) study, neither BP group differed significantly from controls, and in the Dickstein et al. (2006) study, the BP group as a whole performed similarly to controls.

It is of note that in some instances, the studies assessed executive functioning and simple psychomotor speed with tests and/or outcome measures different to those employed in the present investigation. While Dickstein et al. (2004) also employed the SWM test to assess nonverbal working memory, it is noteworthy that the number of total search errors was considered as opposed to the number of between search errors. Given that within search errors are rarely detected in ADHD, it is possible that the total search error outcome measure (which collapses together within and between search errors) was not sensitive enough to detect impairment. Similarly, although Rucklidge (2006) also employed the Digit Span test to assess verbal working memory, she relied on composite scores rather than DSB to detect impairment. Through incorporating DSF, a task which primarily implicates short-term memory storage, the composite score is less sensitive to working memory impairment (Lezak, 2004).

While it is helpful that Pavuluri et al. (2006) also measured cognitive flexibility through considering completion times on the Trail Making Test Part B (TMT-B), Rucklidge (2006) assessed this cognitive function using an alternative trail making paradigm (Color Trails 2). This is significant because under certain conditions Color Trails and the TMT-B may fail to assess equivalent constructs. In healthy individuals, strong correlations between both tests

have only been detected in older participants (35 to 54 years) who have high levels of education (12 to 22 years of education) (Lee & Chan, 2000). It is significant that Dickstein et al. (2004) employed the CANTAB Intra/Extradimensional Shift (IES) test whereas Rucklidge (2006) and Mattis et al. (2011) used the Wisconsin Card Sorting Test (WCST), to assess for cognitive flexibility. Such tasks largely mirror each other and in healthy populations, performance on these measures tends to correlate with performance on the TMT-B (Sanchez-Cubillo et al., 2009). Nevertheless, meta-analytic research suggests that the WCST is likely to be associated with smaller effects than the TMT-B in adult ADHD (Hervey et al., 2004). It is significant that Pavuluri et al. (2006) also employed the Cogtest Set Shifting paradigm to assess cognitive flexibility as its convergent validity with other measures, including the TMT-B does not appear to have been ascertained. Like the present study, the Mattis et al. (2011) and Pavuluri et al. (2006) studies also assessed verbal fluency using the Controlled Oral Word Association test. Unlike this study, however, it is important to note that the executive functioning composite measure employed by Pavuluri et al. (2006) was also based on a test of problem solving (the Penn Conditional Exclusion Test). Indeed, problem solving is an executive functioning skill that was not explicitly assessed in the present study.

Like the present investigation, Rucklidge (2004) and Mattis et al. (2011) also failed to detect differences between BP with and without comorbid ADHD groups on measures of inhibition as indexed by commission error rates on a CPT. Making parallels between such results may be problematic however as Rucklidge (2004) and Mattis et al. (2011) employed the Conners' CPT which has a higher signal probability than the RVIP. Indeed, it is traditionally associated with much larger commission error rates in ADHD (Boonstra et al., 2005; Hervey et al., 2004). Unlike the present study, the Mattis et al. (2011) and Rucklidge (2006) studies also employed the Color-Word condition of the Stroop test to evaluate inhibition. This measure is presented in a completely different format to a CPT. In the Rucklidge (2006) study, it is

noteworthy that only the BP with comorbid ADHD group was impaired relative to controls on this measure as meta-analytic research suggests that slightly larger effects have been found using this test in ADHD relative to the Conner's and more traditional CPTs (Boonstra et al., 2005; Hervey et al., 2004). Unlike Dickstein et al. (2004), who used the same measure of simple psychomotor speed (MS) as the present investigation, Pavuluri et al. (2006) used the test of finger tapping speed from the Cogtest battery. Unfortunately, there are no studies available which have compared these two tests. Given that children and adults both demonstrate remarkably similar levels of executive dysfunction regardless of whether they have ADHD or BP (refer to Age and Developmental Aspects of Neuropsychological Functioning sub-section), it is probably not that significant that the current study included a slightly older sample than these other studies.

To help place the results for the two BP groups in context, attention will now be given to the results from other studies of adult BP which employed similar measures of executive functioning and simple psychomotor speed (but may have failed to control for the effects of lifetime ADHD). In general terms, it is surprising that the BP groups performed similarly to controls on measures of executive functioning as meta-analytic studies of adult euthymic phase BP have detected significant effects for this domain using the same cognitive flexibility, auditory working memory, and verbal fluency outcome measures as the present study (Arts et al., 2007; Bora et al., 2009; Kurtz & Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006; Tores et al., 2007). Although it is surprising that neither BP group was impaired on a measure of spatial working memory, further research is required because while one study detected effects for this measure in euthymic phase BP (Barrett et al., 2008), another study did not (Clark et al., 2002). Whilst it is somewhat surprising that the two BP groups performed similarly to controls on a measure of inhibition, this is broadly consistent with the results of other studies which applied this measure to euthymic phase BP groups

(Clark et al., 2002; Clark et al., 2005; Maalouf et al., 2010). As discussed, larger meta-analytic effects for inhibition have tended to be detected on the Conner's CPT due its higher signal probability (see above) (Boonstra et al., 2005; Hervey et al., 2004). It was not particularly surprising that simple psychomotor speed was not compromised in the BP+childhood ADHD group as most studies of BP (Dickstein et al., 2006; Pavuluri et al., 2006) and ADHD (Hervey et al., 2004) have failed to detect effects for such tasks or have only detected small effects.

The absence of higher order cognitive problems in the ADHD-only group supports the argument made by some investigators that such weaknesses and frontal lobe dysfunctions in particular are not a precondition for all cases of ADHD (Wilcutt et al., 2005). Although the results were not significant, it is noteworthy that large effects were present for the ADHD-only group relative to controls on tests that measured working memory and cognitive flexibility. Indeed, the mean scores for the ADHD-only group on such measures largely paralleled those reported for ADHD groups in other studies (Chamberlain et al., 2007; Hervey et al., 2004; McLean et al., 2004). Hence, the potential impact of comorbid ADHD on executive functioning in BP may require some further consideration.

It is noteworthy that there were no group effects on the CANTAB Motor Screening (MS) test as this in turn helps to make clear the important distinction between simple psychomotor speed and processing speed as it applies to ADHD and BP. Measures of basic psychomotor speed, including the MS test rely more on low level information processing loads as well as basic perceptual skills and coordination. Consistent with the results of other studies of ADHD (Hervey et al., 2004) and BP (Dickstein et al., 2004; Pavuluri et al., 2006; Braw et al., 2007; Sweeney et al., 2000), the present investigation detected no impairment on this measure of simple psychomotor speed. Tests that seek to explicitly measure processing speed or mental activity tend to involve high levels of verbally mediated processing and/or choice or

discrimination skills. Other research suggests that the processing speed skill domain is more likely to be associated with impairment in both ADHD (Frazier et al., 2004; Boonstra et al., 2005; Hervey et al., 2004) and BP (Bora et al., 2009; Kurtz & Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007; Mann-Wrobel et al., 2011; Arts et al., 2008). Although not explicitly tested, the findings of this study provide some indirect evidence that ADHD in particular may be associated with processing speed difficulties. Specifically, this group demonstrated its greatest levels of impairment on tasks that involved verbally mediated processing, including the use of encoding strategies: the RAVLT short-term memory, learning, and long-term memory conditions, as well as the DMS test.

Implications of the Research and Future Directions

The results of this study may help to guide future research as they suggest that childhood ADHD may only impact on cognitive functioning in BP if it is confirmed as being comorbid. Future studies need to test this hypothesis by comparing adult BP with comorbid ADHD, BP-only, ADHD-only, and control samples on a range of neuropsychological measures. As indicated in the Limitations sub-section, the quality of assessment procedures in the present study were unfortunately such that a significant proportion of the BP+childhood ADHD group may have lost their ADHD diagnoses as adults.

This study contributes to the literature through supporting the results of neuroimaging studies that detect more diffuse neurological impairment in ADHD versus BP samples (Passarotti et al., 2010). Indeed, it was a group with current ADHD that demonstrated the most widespread neuropsychological impairment. Indeed, while the ADHD-only and BP-only groups were both impaired on measures of sustained attention and short-term spatial memory, the former group was also impaired on measures of verbal declarative memory, and short-term visual object memory. In light of these findings, it is plausible that the presence of comorbid ADHD

may widen the range of cognitive impairment in BP. Future study's need to test this hypothesis by comparing adult BP with comorbid ADHD, BP-only, ADHD-only, and control samples on a wide range of neuropsychological measures. It is particularly significant that performance on measures of verbal declarative memory, and short-term visual object memory are sensitive to the use of encoding strategies. Indeed, the results of the present study suggest that future research should be conducted to explore whether encoding deficits are a trait marker of ADHD, and whether their presence can be used to help differentiate this syndrome from BP.

Another important finding of this study is that it found evidence that BP can be associated with neuropsychological impairment even after controlling for ADHD. This is an important finding in its own right. Indeed, mental health professionals and researchers should consider the potentially negative impact that attention and memory difficulties may be having on treatment response and the day-to-day functioning of individuals with BP, including their work and social functioning.

The study also provides a contribution to the literature on aetiology for BP and ADHD. Although there may be a trend for ADHD groups to be more neurocognitively impaired than BP groups, it is likely that both syndromes share some underlying neurological features. This is suggested by the fact that both groups were similarly impaired on measures of sustained attention and short-term spatial memory, and performed similarly across all five tests of executive function and a measure of simple psychomotor speed. Also, the findings of the present study reinforce the distinction between simple psychomotor speed and processing speed as it applies to ADHD and BP. Consistent with the results of other research, psychomotor speed seems to be spared whereas processing speed may be compromised in

both of these syndromes. The contribution of ADHD to processing speed in BP certainly requires further research as it was not a focus of the present investigation.

Prior to this investigation, the results of various studies gave support to the notion that the presence of lifetime ADHD may at the very least partially contribute to neuropsychological impairment in BP. Importantly, the findings from the present study suggest that this may be less likely if a wide range of relevant clinical and non-clinical variables are systematically covaried. The studies that failed to control for such covariates are identified in the Limitations of Past Research section. Given that IQ is known to impact negatively on verbal declarative memory (Bora et al., 2007; Ferrier et al., 1999), nonverbal memory (Lezak, 2004), and executive functioning (Denckla, 1996), it is significant that the present study controlled for this covariate when numerous other neuropsychological studies of BP (including those that did and did not control for lifetime ADHD) did not. In the present study, this proved to be significant as one of the group effects for the verbal declarative memory domain (delayed verbal recognition memory) disappeared after covarying IQ. Similar neuropsychological studies should thus endeavour to control for this covariate in the future.

It is also noteworthy that this was the first study of its kind to control for the impact of child abuse even though this variable was not shown to influence group effects. This represents a methodological strength as high rates of child abuse are typically found within BP populations (Garno et al., 2005; Hyun et al., 2000; Leverich et al., 2002), and child abuse is often associated with verbal declarative memory problems. It is also helpful that the present study was one of the few to include a measure of lifetime psychotic phenomena as this too has been shown to interfere with verbal declarative memory (Bora et al., 2007) and executive functioning (Bora et al., 2010). Similarly, the present investigation has an advantage over similar studies as it controlled for the potential negative effects of the medications typically

used to treat BP. Indeed, such medications have been shown to interfere with verbal declarative memory (Amado-Boccaro et al., 1995; Balanza-Martinez et al., 2010; Honig et al., 1999; Patchet & Wisniewski, 2003). As detailed in the Limitations of Past Research section, many studies of BP, particularly those that used the RAVLT but neglected to control for lifetime ADHD, failed to control for medication.

It is notable that the present study considered the impact of mood symptoms as statistically significant group effects on measures of psychomotor speed and two short-term spatial memory outcome measures were no longer present after controlling for depressive symptoms. This is consistent with the results of BP research that failed to control for lifetime ADHD. Such research reveals that mood state has the potential to impact on declarative verbal memory (Kurtz & Gerraty, 2009), nonverbal memory (Braw et al., 2007; Roiser et al., 2009; Rubinsztein et al., 2006; Sweeney et al., 2000), and sustained attention (Kurtz & Gerraty, 2009). In light of these findings, it is problematic that two neuropsychological studies of BP that controlled for the effects of lifetime ADHD failed to explicitly control for the effect of residual mood symptoms (see Limitations of Past Research section).

Whereas nicotine consumption (Barr et al., 2008) has been associated with sustained attention and executive functioning performance, caffeine consumption (Lieberman et al., 2002) has also been shown to impact on sustained attention in healthy adults. In light of such findings, it is helpful that the present study attempted to covary these variables even though they did not influence the results. Indeed, no other studies of BP (including those that did and did not control for lifetime ADHD) have controlled for the effects of these variables on sustained attention or executive functioning. It is also notable that the present study controlled for the potential effects of learning disorders on executive functioning. Indeed, no other study of BP (including those that did and did not control for lifetime ADHD) included such a measure. Interestingly, the present study found that group effects on measures of psychomotor speed

and two short-term spatial memory outcome measures disappeared after controlling for learning difficulties. Henceforth, similar neuropsychological studies should also attempt to control for this covariate in the future.

An additional strength of the current study was that it applied less stringent exclusion criteria to each group relative to a number of similar studies. This enhanced the external validity of the findings as current or lifetime Axis I diagnoses were detected at rates similar to those reported for the general New Zealand population (except for those Axis I diagnoses which were included as exclusion criteria (see Table 5) (Wells et al., 1989). Also, the presence of group effects on cognitive measures was underscored as they occurred in the presence of a control group with psychiatric features. As suggested in the Limitations of Past Research section, it is more difficult to detect group effects on cognitive measures if a control group has comorbid disorders, including substance dependence (Levy et al., 2008) or anxiety disorders (Hsiao et al., 2009). As detailed in the Limitations of Past Research section, the current study was largely unique in that many neuropsychological studies of BP have applied stringent inclusion criteria to control groups (including those that did and did not control for lifetime ADHD).

In clarifying whether ADHD contributes to neuropsychological impairment in BP, it is most helpful if studies that include BP with and without lifetime ADHD groups compare such groups to ADHD-only groups and control groups. Other than the present study, only Rucklidge (2006) has compared all four groups on measures of neuropsychological function. Whereas McClure et al. (2005) compares the two BP subgroups to a control group, Mattis et al. (2006) compares the two BP subgroups to an ADHD-only group. Pavuluri et al. (2006) and Dickstein et al. (2004) fail to compare each BP subgroup to ADHD-only or control groups.

Of all the neuropsychological studies which have compared BP with and without lifetime ADHD (Dickstein et al., 2004; Mattis et al., 2006; McClure et al., 2005; Pavuluri et al., 2006; Rucklidge, 2006), the present study is unique in that it was the first to look explicitly at young adults. The other five studies included child/adolescent samples. This point of difference is significant when one considers that adults in particular who have BP with a history of ADHD demonstrate significantly more interpersonal violence, suicide attempts, and legal problems, as well as poorer social functioning than individuals with BP alone (Ryden et al., 2009; Nierenberg et al., 2005; Sentissi et al., 2008).

The results inadvertently provided a further contribution to the literature in that they confirmed previous findings of severe clinical impairment in young BP adults with childhood ADHD. Consistent with other studies, such individuals demonstrated higher rates of manic episodes, an earlier BP and depression onset, and a longer BP duration. Further research is needed to determine whether this BP subgroup represents a distinct bipolar phenotype. The results suggest that mental health professionals should be knowledgeable of this constellation of symptoms, and be able to modify their treatment approaches accordingly.

Limitations

The present study was associated with a number of methodological limitations: the quality of assessment measures, the validity of various covariate indicators, and the absence of other significant covariate measures. Also, the sample source for the two BP groups was such that the results may not generalise to the wider psychiatric population. The procedure for diagnosing ADHD in the BP+childhood ADHD group was weaker than that employed by other neuropsychological studies that compared BP with and without lifetime ADHD. Diagnoses of ADHD are most reliable when they include current and lifetime symptom information and are based on information obtained from multiple informants and symptom

rating scales. Unfortunately, the present investigation did not measure current ADHD symptoms and retrospectively assessed for childhood ADHD with a modified version of a semi-structured clinical interview (the Schedule of Affective Disorders and Schizophrenia-Lifetime Version or SADS-L) that relied solely on self-report. While the psychometric properties for this instrument are unclear, it is noteworthy that the test-retest reliability coefficients for a similar instrument (the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version or K-SADS-PL) are only within the “good range” for ADHD (.63) (Kaufman et al., 1997). Henceforth, it may have been more difficult to detect the potential cognitive effects of ADHD in the BP+childhood ADHD group because in some cases, symptoms that resembled ADHD during childhood may more appropriately have been subsumed under BP alone or under an alternative diagnostic category such as an anxiety disorder. With this being said, it is worth noting that the Psychotherapy for Bipolar Disorder Study (PBDS) did attempt to minimise this risk through administering an extensive initial evaluation of BP. Compared to the present study, Rucklidge (2006) conducted a significantly more comprehensive assessment of ADHD (both current and lifetime) which consisted of a parent and adolescent semi-structured clinical interview (Schedule of Affective Disorders and Schizophrenia for School-Age Children-Present Episode and Lifetime Version or K-SADS-PL), and the completion of ADHD symptom rating scales (Conners’ Rating Scales-Revised and Child Behavior Checklist) by the parents and teachers of participants. The McClure et al. (2005), Pavuluri et al. (2006), Dickstein et al. (2004) and Mattis et al. (2006) studies assessed for current ADHD through obtaining information from the K-SADS-PL, which they administered separately to participants and their parents.

In the present study, the validity and thus sensitivity of various covariate measurements was unknown which in turn may have increased the likelihood of both type I and type II errors.

The presence of childhood abuse is known to impact negatively on a variety of cognitive skills: verbal declarative memory (Savitz et al., 2008), and nonverbal memory (Savitz et al., 2008). Unlike the Savitz et al. (2008) study, the present investigation did not use a validated measure (e.g. the Childhood Trauma Questionnaire) to control for the potential cognitive effects of sexual, emotional, and/or physical abuse. Rather, a dichotomous variable was developed based on information obtained from two separate semi-structured interviews (the CAADID for ADHD and control groups, and supplementary questions in the SCID for BP-only and BP+childhood ADHD groups). The empirical validity of this measure is currently unknown.

The number of lifetime manic episodes has also been associated with poorer performance in various cognitive skill areas: verbal declarative memory (Cavanagh et al., 2002; Martinez-Aran et al., 2004; Deckersbach et al., 2004), nonverbal memory (Deckersbach et al., 2004), sustained attention (Bora et al., 2007; Clark et al., 2002), and executive functioning (Van Gorp et al., 1998; Zubieta et al., 2001). Whereas these other studies have included a continuous measure to assess the number of manic episodes, this was not possible in the present study as investigators in the PBDS had included the code “10+” to identify participants with 10 or more manic episodes. As a consequence, the present study developed a yes/no variable that identified individuals with 10 or more manic episodes. The empirical validity of this measure is currently unknown.

The presence of learning disorders is also known to impact on cognitive functioning, particularly executive functioning (Seidman, 2006). Unfortunately, the present study failed to include a comprehensive assessment of learning disorders, including semi-structured interviews and achievement tests (e.g. the Wide Range Achievement Test 4). Rather, a dichotomous variable was employed which sought to ascertain whether significant learning

difficulties had been present during childhood. Unfortunately, the validity and reliability of this measure is unknown.

It should also be noted that the current study failed to control for the potential cognitive effects of other disruptive behavioural disorders, including oppositional defiance disorder and conduct disorder. Given that these comorbid diagnoses are relatively common in ADHD, it would have been desirable if such syndromes had been explicitly assessed for with semi-structured interviews and/or specific psychometric tests. It is also notable that the present study failed to include a validated test of socio economic status (SES) (e.g. the New Zealand Socioeconomic Index of Occupational Status) as low SES is sometimes associated with poorer cognitive outcomes, including executive dysfunction (Noble et al., 2005). Nevertheless, given that one's education level is often associated with SES, it is of note that the four groups did not differ significantly in terms of years of education.

Given that the BP-only and BP+childhood ADHD groups were recruited from a psychotherapy study (detailed in the Overview of the Psychotherapy for Bipolar Disorder Study sub-section), the results may not generalise to the wider psychiatric population. Indeed, none of the other neuropsychological studies of BP that controlled for the effects of lifetime ADHD recruited participants from a psychotherapy study. Whereas McClure et al. (2005) and Dickstein et al. (2004) recruited participants through a research clinic, Rucklidge (2006) recruited clinical groups through a specialised service that assesses and treats youth with moderate to severe psychiatric disorders. Whilst Pavuluri et al (2006) recruited clinical groups from a clinical drug trial, Mattis et al. (2011) recruited individuals with BP through a web based research programme (the Juvenile Bipolar Research Foundation). It is plausible that individuals with BP may have been excluded from entering the PBDS if they demonstrated certain clinical features (some of which are known to impact on cognitive functioning) that may have made psychotherapy impractical or inappropriate (e.g. multiple

comorbid disorders and/or severe mood dysregulation). Further, given that widespread cognitive impairment may “limit engagement and response to cognitively demanding forms of psychotherapy”, it is plausible that individuals who appeared to demonstrate such impairment at screening were excluded from the PBDS (Rubinsztein et al., 2006, p. 637). Concerns about the present study’s sample source may, however, be overstated, as the PBDS used few exclusion criteria. Indeed, compared to the BP with and without lifetime ADHD groups recruited in the McClure et al. (2005), Rucklidge (2006), Pavuluri et al. (2006), and Mattis et al. (2011) studies, the BP groups recruited in the present investigation demonstrated higher rates of clinically significant mood symptoms at the time of cognitive testing. As explained in a previous section (The Contribution of Lifetime Comorbid ADHD to Neuropsychological Functioning in Bipolar Disorder), this is of note given that the severity of mood symptoms tends to be associated with worse neurocognitive outcomes.

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Appendix A

Psychotherapy for Bipolar Disorder Study

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Psychotherapy for Bipolar Disorder Study

Information Sheet

Introduction

You are invited to take part in a clinical treatment trial for young people (ages 15 to 34) with bipolar disorder, being conducted by Professor Peter Joyce, Dr Sue Luty, Dr Janet Carter, Dr Stephanie Moor, Dr Marie Crowe, Dr Jane O'Malley, Maree Inder, Robyn Abbott, Andrea Bartram, Dr Martin Kennedy, Helen Kleindienst, Jason Brown and Dr Sam Ritz.

The major goal of this project is to improve the way we help you manage your bipolar illness. We believe that the addition of psychotherapy to medication improves outcome but we are not sure which psychotherapy is best. Thus, in this study we aim to compare two different psychotherapies, in conjunction with medication, in the treatment of bipolar disorder. The two psychotherapies to be investigated in this study are called interpersonal social rhythm therapy (IPSRT) and specialist supportive care (SSC). In interpersonal social rhythm therapy the focus will be on the relationship between bipolar disorder and interpersonal relationships and how to make changes in interpersonal relationships to improve well being and relieve symptoms. In specialist supportive care the focus will be on education about bipolar disorder, improved recognition of mood, early identification of changes in mood, and dealing with the consequences of bipolar disorder. In addition to the psychotherapy you will also be prescribed appropriate medication for your bipolar disorder.

Each of the therapies will be offered to you over a period of 18 months. Sessions will likely be weekly initially, and also during times when you are more unwell. After the initial weekly sessions, the frequency will vary to between fortnightly and monthly depending upon how well you are, and your wishes. In addition to the psychotherapy sessions you will have regular appointments with the psychiatrist or psychiatric registrar who is prescribing your medication.

Your participation in this study is voluntary (your choice). If you agree to take part you may withdraw at any time and for any reason. If you do not participate or withdraw from the study, this will not affect your future health care.

More about this study

What are the aims of this study? We plan to determine whether interpersonal psychotherapy or specialist supportive care is the better type of psychotherapy for an individual with bipolar disorder.

Who can participate in this study? If you have bipolar disorder, and are age 15 to 34 years, you may participate in this study.

What is bipolar disorder? Bipolar disorder, also called manic depression, is a mood disorder in which individuals suffer from episodes of depression and episodes of mania or hypomania. In depressive episodes people lack energy, lose interest and enjoyment in usual activities, feel sad and hopeless, have disturbed sleep and appetite, cannot concentrate and may have thoughts of death or suicide. During manic or hypomanic episodes, people usually have increased energy and drive, a

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decreased need for sleep, experience racing thoughts, may speak faster and louder, feel euphoric or irritable, and may be over-confident or grandiose. In a manic episode these symptoms cause significant difficulties for the person or those around them; while in hypomanic episodes these symptoms do not cause significant problems.

How will participants be selected for this study? If you have bipolar disorder, and are 15 to 34 years of age you may participate. Some people may be referred by their general practitioner, or from mental health professionals. You may also contact the Clinical Research Unit yourself if you suffer from bipolar disorder.

How many participants will be involved? We hope to recruit about 150 people.

Where will the study be held? The major location for all the assessments, psychotherapy sessions and medication visits will be at Terrace House, near Christchurch Hospital.

What is the time span for the study? Treatment, with both psychotherapy and medication, will be offered over a period of 18 months. Following the 18 months of treatment we would like to follow your progress for up to 5 years.

What will happen during the study? The first step in the study will usually involve a brief telephone conversation with a research nurse. During this telephone conversation the nurse will gather brief information about your bipolar disorder, who has referred you to the study and who is currently providing treatment to you. The nurse will then give you some information about the study and arrange an initial appointment time.

This initial appointment will be with either the psychiatrist or psychiatric registrar (who will prescribe you medication during the study) or with your potential psychotherapist for the study. During this initial assessment information will be obtained about you and your bipolar disorder. You will also be given more information about the study and given the opportunity to ask questions about the study. At the end of the assessment you will be given a consent form for participation in the study.

After you have given consent to participate we will organise with you:

- a. An initial (and ongoing) psychotherapy session. Which psychotherapy you receive will be determined randomly (i.e. "by the flip of a coin").
- b. An appointment with your psychiatrist or psychiatric registrar, who will complete a detailed assessment of your bipolar disorder and associated factors, and review your medication.
- c. A time to meet with you and your family and /or friends. Subject to your consent we will also meet with them separately to obtain further history about your bipolar disorder and associated factors.
- d. A day for a blood test and other tests which may be relevant to your bipolar disorder. During this day of tests, the research nurse will also systematically collect information on how your bipolar disorder has been over the past six months.

After these initial sessions you will:

- a. Have regular psychotherapy sessions over the next 18 months. Initially, these are likely to be weekly, but over time, and depending upon your needs and wishes, the frequency of sessions will decrease. In some situations these may end up as monthly sessions.
You will be asked if you consent to having the psychotherapy sessions audiotaped. This is to ensure a high quality of treatment. Some audiotapes may be heard by other members of the research team. You have the option of stopping the taping or having the tapes destroyed. In

- selected instances, we may also ask for some sessions to be videotaped. As with audiotaping you have the option of stopping videotaping or having the tapes destroyed.
- b. Have regular sessions, probably fortnightly, monthly or two monthly, with your psychiatrist or psychiatric registrar. During these sessions there will be a review of your progress and current state, ongoing discussion and education about your bipolar disorder, and medication will be reviewed.
 - c. Every six months the research nurse will contact you to review how you and your bipolar disorder have been over the past six months. These reviews will therefore happen after six, twelve and eighteen months. The research nurse will also review your progress after the 18 months of treatment is completed.
 - d. At the end of the 18 months of treatment we will ask you to repeat the day of blood and other tests which you completed at the beginning of the study.

What is involved with these tests? At the beginning of the day we will take a blood test to check your current health status. The test will include a blood count, thyroid tests, liver and kidney tests, glucose, cholesterol and vitamin levels.

We will ask you to empty your bladder, and then we will give you a nasal spray of vasopressin. Two hours later we will collect a further urine sample from you, to test how the vasopressin (a brain hormone which influences kidney function) has affected your kidneys.

In the morning, around lunchtime and during the afternoon we will collect saliva samples from you, to measure stress hormones, such as cortisol.

During the day we will ask you to complete a number of self report questionnaires which will cover areas such as your symptoms, how you have been functioning in recent weeks, your personality and coping mechanisms, and questions about your childhood.

We will also ask you to undertake some tests on a computer. One test measures how often you "switch" between using the left side and the right side of your brain. Another test assesses your ability to recognise various emotions such as anger, happiness, sadness and disgust in faces that will be shown to you on a computer screen. The third test involves a series of measures of your attention, concentration and memory.

Genetic tests. From the blood we will also extract and store DNA (genetic material). Each person has a DNA make-up (their genes) which is different from that of everybody else (except in cases of identical twins). This genetic make-up comes in part from your mother and in part from your father. We already know that bipolar disorder runs in families although at this time we are not sure exactly which genes are involved. In addition to genes contributing to the cause of bipolar disorder, specific genes may influence aspects of bipolar disorder such as specific symptoms or the age at which it develops. Genes may also influence aspects of your personality, such as your tendency to be a worrier, or a perfectionist, or to be impulsive. Genes may also influence whether you respond to specific drugs, such as lithium or an antidepressant, and genes may influence whether you get specific side effects from the drugs we prescribe for your bipolar disorder.

DNA samples will be identified only with a code, and, as with all other material gathered in this research, will be confidential and will not be disclosed or used in any way without your informed consent. The DNA samples will be kept until recruitment and treatment is completed and for a further five years to allow all tests to be completed. The samples will be used only for the purposes of the study. If you decide to withdraw your consent to the storage of your DNA samples during the storage period, you may do so by contacting the Clinical Research Unit, ph 372 0400, or by writing to the address at the end of this Information Sheet.

Will my GP know I am in the study? We prefer to advise your GP that you are involved with this treatment study, however, this is your decision.

Risks and Benefits

The major benefit for participants is that they will receive free high quality psychotherapy plus medication management of their bipolar disorder over a period of eighteen months.

From your participation in the study we may learn more about bipolar disorder, and this may ultimately help other people with the same disorder.

We do not envisage any major risks with this treatment research project. Having bipolar disorder increases risk for a variety of adverse outcomes, and not receiving treatment for bipolar disorder also increases risks for adverse outcomes; also the acceptance and talking about your life and your bipolar disorder may sometimes be distressing. Having blood tests may be associated with some discomfort and bruising.

If you choose to participate in this study, there may be repercussions from you and for your whanau/family because you have given away genetic information. Whilst the sample given is from you, it will contain information shared by other whanau/family members and they may consider you do not have any right to give that information to others. Te Runanga O Ngai Tahu does not support genetic research.

Participation

- Your participation in this study is voluntary (your choice).
- If you agree to take part, you are free to withdraw from this study at any time.
- If you choose not to take part or to withdraw, this will not affect any of your future health care. We will refer you back to your general practitioner or other mental health services as appropriate.
- While we anticipate that most treatment will occur on an outpatient basis at Terrace House; if you become unwell admission for inpatient care will be organised for you.
- In extreme situations if you became very unwell, we may have to use the Mental Health Act to ensure your safety and ongoing care, but we hope this is very unlikely.
- If you have any queries or concerns about your rights as a participant in this study you are free to contact a Health and Disability Services Consumer Advocate, Ph. (03) 377 7501.

Confidentiality

With the research data we collect, your data will be identified by an ID number. No material which could personally identify you will be used in any reports based on this study. The data will be available only to the study investigators. All data will be stored in secure areas.

You do not have to answer all the interview questions or every question in the questionnaires.

This programme is conducted within the Clinical Research Unit, in a collaboration between the Christchurch School of Medicine (University of Otago) and the Canterbury District Health Board. Two types of information will be collected from you – *research* information and *clinical* information. Research information is kept in a non-identifying form as described above. Usual CDHB policies and procedures are followed for confidentiality of clinical information.

Results

How can I get results of this research? When this study is over you may have a summary of the key results. Detailed results will be published in international scientific journals.

Compensation

There may be compensation available to you in the unlikely event that you are injured taking part in this research. If you suffer physical injury as a result of your participation in this clinical trial, you may be covered by ACC. You should note, however, that eligibility for cover is not automatic.

You would be in the same position as a claimant who has suffered physical injury as a result of medical error or negligence, or as a result of medical mishap, i.e. an adverse consequence of treatment which is both rare and severe.

If your claim for cover is accepted by ACC, your entitlement to compensation would depend on a number of factors, such as whether you are an earner or non-earner. You should note that in most cases ACC provides only partial reimbursement of costs and expenses and there is no lump sum compensation payable under current ACC legislation. You should also be aware that if; you have cover under the ACC legislation, your risk to sue the researcher(s) or anyone else involved in the clinical trial is extremely limited. If you have any questions about cover or entitlements under the ACC scheme, you should contact your nearest ACC branch office for further information before you consent to participate in this trial.

This study has received ethical approval from the Canterbury Ethics Committee.

Where can I get more information about the study? **Robyn Abbott** may be contacted by telephone or by letter: Clinical Research Unit, University Department of Psychological Medicine, Terrace House, 4 Oxford Terrace, Christchurch, Ph. 372 0400, Fax. 372 0407.

Appendix B



CHRISTCHURCH SCHOOL OF MEDICINE & HEALTH SCIENCES
DEPARTMENT OF PSYCHIOLOGICAL MEDICINE

Telephone (03) 372 0400

Fax (03) 372 0407

Clinical Research Unit
Terrace House
4 Oxford Tee
Christchurch

Psychotherapy for Bipolar Disorder Study Consent form

Investigators: Professor Peter Joyce, Dr Sue Luty, Dr Stephanie Moor, Dr Janet Carter, Dr Marie Crowe, Dr Jane O'Malley, Maree Inder, Robyn Abbott, Andrea Bartram, Dr Martin Kennedy, Helen Kleindienst, Jason Brown and Dr Sam Ritz.

I have read and heard about this study, and understand what is involved.

I have been given the opportunity to discuss this study and to ask questions about it. I am satisfied with the answers I have been given.

I have had enough time to consider whether to take part, and to discuss my decision with a person of my choice.

I know whom to contact if I have questions about the study.

I understand that:

- My taking part in this study is voluntary.
- I am free to withdraw at any time and for any reason.
- I have read and understand the compensation statements on the information sheet.
- I understand that I will be interviewed, be asked to complete questionnaires, to have blood tests and computer tests that are relevant to my bipolar disorder.
- I will be asked to be seen with family and/or friends, and I understand that they will be asked questions about me.
- The taping of psychotherapy sessions is for research purposes and some tapes may be heard by other members of the research team.
- I have the option of stopping taping or having the tapes destroyed.
- My participation in this study is confidential and no information that could identify me will be used in any reports on this study.
- This study has received ethical approval from the Canterbury Ethics Committee.

I consent to take part in this study YES / NO

I consent to having my psychotherapy sessions audiotaped YES / NO

I consent to having some psychotherapy sessions videotaped YES / NO

I consent to have my General Practitioner contacted regarding my participation YES / NO

I am aware that the study will examine my DNA (genetic material) to look for associations between aspects of my bipolar disorder and specific genes.

I understand that I can request to have my DNA destroyed prior to the planned time for destruction of all DNA which is five years after treatment is completed.

I consent to such genetic analyses being performed YES / NO

I wish to receive copies of newsletters which will contain results of this study YES / NO

I _____ (print full name) hereby consent to take part in this study.

Date: _____

Phone number: _____

Signature: _____

In my opinion, consent was freely given and the participant understands what is involved in this study.

Study Investigator's signature: _____ Date: _____

Study Investigator's name: _____

Contact telephone number: Robyn Abbott (03) 372 0400
Version 1/July 2003

Psychotherapy for Bipolar Disorder Study

Appendix C

23 July 2003

REFERENCE
COPY

Canterbury Ethics Committee

4th Floor, 250 Oxford Terrace
P.O. Box 3877
Christchurch
Phone (03) 372 3018
Fax (03) 372 1015
Email: sally_cook@moh.govt.nz

Professor P Joyce
Department of Psychological Medicine
Christchurch School of Medicine & Health Sciences
P O Box 4345
Christchurch

Dear Professor Joyce

A randomized clinical trial of Interpersonal Social Rhythms Psychotherapy in Young People with Bipolar Disorder

Investigators: Prof P Joyce, Dr S Luty, Dr J Carter, Dr S Moor, Dr M Crowe, Dr J O'Malley

Ethics reference: CTY/03/06/092

Thank you for your response to the points raised by the Committee. I am pleased to advise that, using the delegated authority granted her by the Committee, the Chairperson of the Canterbury Ethics Committee has given final ethical approval for this study to proceed in Canterbury.

The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Please ensure the first statement on the consent form refers to the information sheet version as per point 8 of the Committee's letter ie "I have read or had explained to me the information sheet version 1 /July 2003 for this study and understand what is involved".

Approval is until 30 June 2009. The Committee will review the study annually and notify you if it withdraws approval. It is your responsibility to forward a progress report in June each year. Failure to do so may result in withdrawal of ethical approval. A final report is also required at the conclusion of the study. Report forms are available from the administrator.

It is also a condition of approval that the Committee is advised of any adverse events, if the study does not commence, or the study is altered in any way, including all documentation eg advertisements, letters to prospective participants. Please quote the above ethics committee reference number in all correspondence.

The Committee wishes you well with your research.

Yours sincerely



Sally Cook
Ethics Committee Administrator

Accredited by Health Research Council

Appendix D



Upper South A Regional Ethics Committee

Ministry of Health
4th Floor, 250 Oxford Terrace
PO Box 3877
Christchurch
Phone (03) 372 3037
Fax (03) 372 1015

16 August 2007

Mr Jason Alan Brown
77 Ilam Road
Ilam
Christchurch

Dear Mr Brown,

Neuropsychological functioning in young adults with Bipolar Disease (BP): contribution of Attention-Deficit/Hyperactivity Disorder (ADHD)
Investigators: J Brown, Dr J Carter (Supervisor) Dr J Rucklidge, Prof P Joyce
Locality: Canterbury DHB
Ethics ref: URA/07/02/015

The above study has been given ethical approval by the **Upper South A Ethics Committee**. A list of members of this committee is attached.

Approved Documents

Information sheet and consent form version 5, dated 16.08.07

Certification

The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation

The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Progress Reports

The study is approved until **31 August 2009**. The Committee will review the approved application annually and notify the Principal Investigator if it withdraws approval. It is the Principal Investigator's responsibility to forward a progress report covering all sites prior to ethical review of the project in **August 2008**. The report form is available on <http://www.newhealth.govt.nz/ethicscommittees>. Please note that failure to provide a progress report may result in the withdrawal of ethical approval. A final report is also required at the conclusion of the study.

Requirements for SAE Reporting

The Principal Investigator will inform the Committee as soon as possible of the following:

- Any related study in another country that has stopped due to serious or unexpected adverse events
- withdrawal from the market for any reason
- all serious adverse events occurring during the study in New Zealand which result in the investigator breaking the blinding code at the time of the SAE or which result in hospitalisation or death.

- all serious adverse events occurring during the study worldwide which are considered related to the study medicine. Where there is a data safety monitoring board in place, serious adverse events occurring outside New Zealand may be reported quarterly.

All SAE reports must be signed by the Principal Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. It is assumed by signing the report, the Principal Investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Amendments

All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

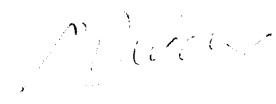
Please quote the above ethics committee reference number in all correspondence.

The Principal Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

We wish you well with your study.

Yours sincerely



Alieke Dierckx
Upper South A Ethics Committee Administrator

Email: alieke_dierckx@moh.govt.nz

List of members of the Upper Region A Ethics Committee, February 2007

Carolyn Mason (Chair)	Ethicist/Philosopher Lay member	Female
Carolynn Bull	Legal representative, Maori representative Lay member	Female
John Horwood	Biostatistician Lay member	Male
Jane Kerr	Researcher Health Professional Member	Female
Alison Luckey	Health Practitioner Health Professional member	Female
Tom Marshall	Clinical Psychologist Health Professional member	Male
Ellen McCrae	Pharmacist Health Professional member	Female
Edie Moke	Maori representative Lay member	Female
Nicky Murray	Community Representative Lay member	Female
Elizabeth Richards	Consumer Representative Lay member	Female
Russell Scott	Health Practitioner Health Professional member	Male

All members were present at the meeting on 26 February 2007.


Alieke Dierckx (Administrator)

Date 26 February 2007

Appendix E

College of Science

Department of Psychology
Tel: +64 3 364 2902, Fax: + 64 364 2181
Email:



Does Attention-Deficit/Hyperactivity Disorder (ADHD) Contribute to Concentration, Memory, and Planning Difficulties in Bipolar Disorder (BP)?

Information Sheet

Principal Investigator:

Jason Alan Brown
Department of Psychology, University of Canterbury, Private Bag 4800, CHRISTCHURCH
Phone: 0212543073 or (03) 3525043
Email: jab150@student.canterbury.ac.nz

Supervisors:

Dr Janet Carter
Room 510, Department of Psychology, University of Canterbury, Private Bag 4800
CHRISTCHURCH
Phone: (03) 3642987, ext. 8090
Email: janet.carter@canterbury.ac.nz

Dr Julia Rucklidge
Room 502, Department of Psychology, University of Canterbury, Private Bag 4800
CHRISTCHURCH
Phone: (03) 3642987, ext. 7959
Email: julia.rucklidge@canterbury.ac.nz

Professor Peter Joyce
Department of Psychological Medicine, Christchurch School of Medicine & Health Sciences,
PO Box 4345
CHRISTCHURCH
Phone: (03) 3720400
Email: peter.joyce@chmeds.ac.nz

Introduction:

You are invited to take part in a student PhD project which examines whether the concentration, memory, and planning difficulties often reported in bipolar disorder (BP) (a mental condition characterised by extreme mood instability) are partly due to a different syndrome known as attention-deficit/hyperactivity disorder (ADHD) (a chronic behavioural disorder of childhood onset). At present, two groups are being recruited, each with 25 members: a group identified as having concentration and attentional difficulties and/or a current diagnosis of ADHD and a control group consisting of individuals without such difficulties.

You will be asked questions about your current and past mental health and will also be asked to complete some computer tasks involving your memory, attention, and planning abilities. It is likely that a total of one or two visits will be necessary, taking up to three or six hours depending on

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Does Attention-Deficit/Hyperactivity Disorder (ADHD) Contribute to Concentration, Memory, and Planning Difficulties in Bipolar Disorder (BP)?

which group you participate in. Your participation in this study is voluntary (your choice). If you agree to take part, you may withdraw at any time and for any reason. If you do not participate or withdraw from the study, this will not affect your future health care.

About the study

What are the aims of the study? To determine whether young adults with BP experience memory, concentration, and planning difficulties due in part to a concurrent history of ADHD. With this regard, four groups will be compared: a group of individuals identified with BP that do not have a history of ADHD (BP-only); a group who have both BP and a history of ADHD (BP+ADHD); a group who only have ADHD (ADHD-only); and individuals in a control group.

How are participants selected for this study, and who selects them? If you are aged between 16 and 34 years and have either a current diagnosis of ADHD or have no current concentration or mood instability problems, you may participate.

Individuals assigned to an ADHD-only group will exhibit concentration difficulties or a current diagnosis of ADHD and will be recruited through either advertisements in a local newspaper, via an existing database at the University of Canterbury, or through advertisements at various Canterbury District Health Board mental health services.

The control group participants will be free of concentration and mood problems and will be recruited from either the general public through public notices or from an existing database at the University of Canterbury.

Why are individuals who have bipolar disorder not being recruited? Individuals with bipolar disorder are being recruited in the *Psychotherapy for Bipolar Disorder Study*, which was established in 2003 by the University of Otago, Christchurch School of Medicine.

How many participants will be involved? It is intended that a group of about 50 (25 in the ADHD-only group and 25 in the control group) individuals will be recruited.

Where will the study be held? Terrace House, near Christchurch Hospital.

What is the time span for the study? If you have no identifiable problems, it is likely that a total of one visit will be necessary, taking up to three and a half hours. If you have difficulties with concentration and/or a current diagnosis of ADHD, two visits will be required with the first taking three hours and the second taking two hours. The assessment takes more time for the latter group as they complete a larger number of tasks.

What will happen during the study? When you contact the primary investigator for the first time by phone, he will initially inform you about the studies aims and any questions will be answered. Also, an appointment for an initial assessment will be scheduled.

If, at the end of the phone conversation, you are willing to participate in the study, you will be sent out an information sheet, a consent form and an appointment time. Also, you will be asked whether a self-report questionnaire and a form which is to be completed by either a friend or family member can be sent out. Each of these forms takes fifteen minutes to complete and assess for the presence and severity of significant ADHD symptoms. Moreover you will be asked whether an additional self-report questionnaire can be sent out which takes between 30 and 60 minutes to complete and includes an assessment of areas such as developmental history, schooling and family history (crucial areas to consider when confirming or disconfirming a diagnosis of ADHD).

Finally, you will be asked whether you would like a support person (e.g. a whanau member or friend) to accompany you at any of the proceeding interviews or assessments. If you consent to a support member being involved, a copy of this information sheet will be sent out to them. You and/or your support person will also have the option of carrying out Karakia (prayers) prior to any of the proceeding interviews or assessments.

ADHD-only group

If you have been assigned to the ADHD-only group and have signed the informed consent form, you will then be interviewed about a wide-range of mental illnesses. The interview will last for three hours. With your approval, the interview that occurs may be video/audiotaped to ensure that the assessment is valid. If you have been diagnosed with ADHD and are currently receiving stimulant medication, you will be asked to refrain from taking stimulant medication for 48 hours prior to the second day of assessment.

On the second day of the assessment, you will complete a series of cognitive tasks lasting 90 minutes which measure memory, concentration, and planning skills. Whilst most of these tasks will involve responding to a computer screen, some will require verbal responses and one will require the use of pencil and paper. You will also be interviewed about your current level of mood for 30 minutes. Moreover, you will be administered a self-report questionnaire that takes fifteen minutes to complete and examines social, interpersonal and occupational functioning.

Control group

If you have been assigned to the control group and have signed the informed consent form, you too will initially complete a series of cognitive tasks lasting 90 minutes which measure memory, concentration, and planning skills. Again, whilst most of these tasks involve responding to a computer screen, some require verbal responses and one requires the use of pencil and paper.

After a short-break, you will be interviewed about a wide-range of mental illnesses for one and a half hours. With your approval, the interview that occurs may be video/audiotaped to ensure that the assessment is valid. You will also be administered a self-report questionnaire that takes fifteen minutes to complete and examines social, interpersonal and occupational functioning.

What will happen to my results? Data collected for the ADHD-only and control samples will be placed in secure cabinets within the Department of Psychology at the University of Canterbury. It will be stored for 10 years.

Benefits, risks and safety

What are the benefits of the study?

ADHD group

If you are in the ADHD-only group, you will receive a \$30 gift voucher and a psychological assessment summary which is based on your interview results. The psychological assessment summary will be posted to you within three weeks of your presenting for the interview and it will provide you with information on your current ADHD symptoms and any other mental health difficulties.

In the proceeding three days after you have received your results, the primary investigator will contact you by phone and explain your results in lay language. He will then get you to verbally feed your results back to him as you understand them and then he will correct, elaborate and/or explain the results as necessary. The primary investigator will then deal with your specific responses to the information. For instance, if you become upset or require assistance, a referral to a GP, Psychiatric Emergency Service, or a mental health service may be forthcoming. In early 2009, you will also receive a general summary of the key findings from this study.

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Does Attention-Deficit/Hyperactivity Disorder (ADHD) Contribute to Concentration, Memory, and Planning Difficulties in Bipolar Disorder (BP)?

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Control group

If you are in the control group, you will also receive a \$30 gift voucher and a psychological assessment summary based on your interview results. In the proceeding three days after you have received your results, the primary investigator will contact you by phone and explain your results in lay language. He will then get you to verbally feed your results back to him as you understand them and then he will correct, elaborate and/or explain the results as necessary. The primary investigator will then deal with your specific responses to the information. For instance, if you become upset or require assistance, a referral to a GP, Psychiatric Emergency Service, or a mental health service may be forthcoming. In early 2009, you will also receive a general summary of the key findings from this study.

What are the risks and/or inconveniences of the study? The risks or side effects from the research are minimal, but include possible psychological distress with structured questions about your life and/or problems. Also, you may find the assessment tiring. Breaks will be offered or the assessment will be rescheduled if necessary. Inconveniences will be time, travel and parking.

Participation

- Your participation in this study is voluntary (your choice).
- If you agree to take part, you are free to withdraw from this study at any time.
- If you choose not to take part or to withdraw, this will not affect any of your future health care.
- Your participation in this study will be stopped should any harmful effects appear or if the principal investigator feels it is not in your best interests to continue/
- You may have a friend, family or whanau support to help you understand the risks and/or benefits of this study and any other explanation you may require.
- If you have any queries or concerns about your rights as a participant in this study you are free to contact a Health and Disability Services Consumer Advocate, Ph. (03) 377 7501.

General

What will happen at the end of the study? If you consent, you will receive a summary of the key results in the mail. This is likely to occur in early 2009.

Will my GP be told I am in the study? It is up to you whether you would like your GP to be contacted regarding your entry into the study. If you are in the ADHD-only group, it is up to you whether or not a summary of your interview results will be sent to your GP.

Where can I get more information about the study? For further information about the study, you may phone Jason Brown on either (03) 3525043 or 0212543073. Alternatively, you can email him at jab150@student.canterbury.ac.nz

If I need an interpreter, can one be provided? No, the memory, attention, and planning tasks require a satisfactory understanding of English.

Confidentiality

- With the research data we collect, your data will be identified by an ID number.
- The data from this research may be useful in future related research projects. If you agree to us using your (anonymous) data in this way, please indicate this on the consent form.
- No material which could personally identify you will be used in any reports based on this study.

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Does Attention-Deficit/Hyperactivity Disorder (ADHD) Contribute to Concentration, Memory, and Planning Difficulties in Bipolar Disorder (BP)?

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- You will have the option of giving the investigators consent to review your mental health records as part of the research process. Mental health records can be distinguished from your general health records in that they refer only to your mental health history and are held at various Canterbury District Health Board mental health services. A review of your mental health records could enhance the accuracy of the assessment process as past mental illness diagnoses may be clarified and medications examined.
- You will have the option of giving the investigators consent to store your name in a separate database so that you can be contacted in the future should there be other studies for you to participate in with the understanding that you can choose whether to participate in such studies or not.
- The data will be available only to the study investigators. It will be placed in secure cabinets within the Department of Psychology at the University of Canterbury.
- Health data will be stored for 10 years within the Department of Psychology at the University of Canterbury.
- The data will be the responsibility of Jason Brown during the study. After he has submitted his PhD, Dr Julia Rucklidge and Dr Janet Carter will be responsible for the data.

Results

How can participants get the results of this research, and where will they be published? When this study is over you may have a summary of the key results. Detailed results will be published in international scientific journals. It should be noted however, that there may be a delay between data collection and publication.

Statement of approval

This study has received ethical approval from the Upper South A Ethics Committee.

Please feel free to contact the principal researcher if you have any questions about this study.

College of Science

Department of Psychology
Tel: +64 3 364 2902, Fax: + 64 364 2181
Email:



Does Attention-Deficit/Hyperactivity Disorder (ADHD) Contribute to Concentration, Memory, and Planning Difficulties in Bipolar Disorder (BP)?

Consent Form

Investigators: Jason Brown, Dr Janet Carter, Dr Julia Rucklidge and Professor Peter Joyce.

- I have read and I understand the information sheet dated 22.11.07 for volunteers taking part in the study designed to determine whether a history of Attention-Deficit/Hyperactivity Disorder symptoms contributes to difficulties with memory, attention, and planning/organisation functions in bipolar disorder.
- I have had the opportunity to discuss this study.
- I am satisfied with the answers I have been given.
- I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.
- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will not affect my future health care.
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
- I understand that the assessment will be stopped if it should appear harmful to me.
- I understand the compensation provisions for this study.
- I have had time to consider whether to take part.
- I know who to contact if I have any questions about the study.

I consent to my interview being video/audio taped.....YES/NO
I consent to the investigators submitting questionnaires which will be completed by a family member or friend of my choosing.....YES/NO
I consent to my mental health records being reviewed.....YES/NO
I wish to receive a copy of the results when available in early 2009.....YES/NO
I agree to my GP (full name: _____) being informed of my participation in this study/the results of my participation in this study.....YES/NO
I agree to my (anonymous) data being used for future related research.....YES/NO
I consent to my name being placed in a separate database so that I can be contacted about other studies in the future. I understand that I can choose whether to participate in such studies.....YES/NO

I _____ (full name) hereby consent to take part in this study.

Date: _____

Signature: _____

Contact details for Jason, the lead investigator: Phone either (03) 3525043 or 0212543073.

Or email at jab150@student.canterbury.ac.nz

Project explained by: _____

Investigator's Signature: _____

Version 6, 22.11.07

Does Attention-Deficit/Hyperactivity Disorder (ADHD) Contribute to Concentration, Memory, and Planning Difficulties in Bipolar Disorder (BP)?

Appendix G

SCID-I Version 2.0 (for DSM-IV) PTSD (FEB 1996 FINAL) modified with CSA addition for CRU Anxiety Disorders
POSTTRAUMATIC STRESS DISORDER

Sometimes things happen to people that are extremely upsetting – things like being in a life threatening situation like a major disaster, very serious accident or fire; being physically assaulted or raped; seeing another person killed or dead, or badly hurt, or hearing about something horrible that has happened to someone you are close to. At any time during your **adult** life, have any of these kinds of things happened to you?

Adult Traumatic Events List

Brief Description	Date (Month/Year)	Age
1.		
2.		
3.		
4.		
5.		
6.		

Sometimes traumatic events happen when people are **quite young**.

CSA1. Did you experience any of these events before you were 16?

Were you the victim/witness of a disaster, accident or war, which affected your ability to live as before

Yes	No	DK
1*	0	9

Before 16, were you ever:

	Number of times				
	0	1*	2-3*	4+*	DK
Threatened with abuse by someone	0	1	2	4	9
Emotionally or psychologically abused	0	1	2	4	9
Beaten so badly you had to see (or should have seen) a doctor	0	1	2	4	9
Other. Specify:	0	1	2	4	9

CSA2. When you were under 16, were you ever physically or psychologically forced by anyone to engage in any unwanted sexual activity, such as unwanted sexual touching of your body or sexual intercourse?

Yes	1*
No	0
DK	9

CSA3. Did this involve: (If DK, code 99; If >87, code 87)

	No. of times		
Someone exposing the sex parts of their body to you when you didn't want it?			
Someone threatening to have sex with you?			
Someone touching the sex parts of your body when you did not want this?			
Someone trying to have sexual intercourse with you when you didn't want this?			
Someone sexually attacking or raping you?			
Other unwanted sexual activity. Specify:			

?=inadequate information

0=absent or false

1=threshold or true

IF ANY CHILD EVENTS (RESPONSES WITH * IN CSA1 AND CSA2) GIVE DETAILS BELOW.

<u>Child Traumatic Events List</u>		
Brief Description	Date (Month/Year)	Age
1.		
2.		
3.		
4.		
5.		
6.		

IF ANY EVENTS LISTED: Sometimes these things keep coming back in nightmares, flashbacks, or thoughts that you can't get rid of. Has that ever happened to you?

IF NO: What about being very upset when you were in a situation that reminded you of these terrible things?

IF NO ADULT OR CHILD EVENTS, CHECK HERE ____ AND GO TO *ANOREXIA NERVOSA* H.1.

____?=inadequate information ____0=absent or false ____1=threshold or true

Appendix H

PHYSICAL HEALTH

A. HEADACHES/MIGRAINES:

No

Yes

Do you suffer from headaches? 0 1

IF NO, SKIP TO
HEAD INJURIES

IF YES:

Have you had at least five severe headaches? 1

IF NO, SKIP TO
HEAD INJURIES

Do you think they are:.....

☐

1. Migraines
2. Tension headaches
3. Both
4. Other

IF MIGRAINE (either alone or with headache):

On which side of the head do they usually occur?..... Left Right
Both

IHS CRITERIA FOR MIGRAINE WITHOUT AURA:

B. Do they last 4 to 72 hours (untreated or successfully treated)	0	1
C. Headache has at least 2 of the following characteristics	0	1
1. Unilateral site		
2. Pulsating quality		
3. Moderate to severe intensity		
4. Aggravation by walking stairs or similar routine physical activity		
D. During headache, at least 1 of the following symptoms:	0	1
1. Nausea and/or vomiting		
2. Photophobia and phonophobia		
E. No evidence of related organic disease	0	1
A. At least five attacks that fulfill criteria in B, C, D and E	0	1

Criteria A, B, C, D and E fulfilled 0

IF NO,
SKIP TO
HEAD
INJURIES

MIGRAINE
WITHOUT AURA

ASK ABOUT
MIGRAINE WITH
AURA

HIS CRITERIA FOR MIGRAINE WITH AURA:

B. At least 3 of the following characteristics:

1. One or more fully reversible aura symptoms indicating focal Cerebral cortical and/or brain stem dysfunction
2. At least one aura symptoms developing gradually over more than 4 minutes or, two or more symptoms occur in succession
3. No aura symptom lasts more than 60 minutes. If more than one aura symptoms is present, accepted duration is proportionally increased.
4. Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura).

C. No evidence of related organic disease 0 1

A. At least 2 attacks fulfilling B 0 1

Criteria A, B and C fulfilled 0 1

|

MIGRAINE WITH AURA

B. HEAD INJURIES:

1. Have you ever had a serious head injury? 0 1

IF NO, SKIP TO
VISION

IF YES:

2. How many times have you had a serious head injury?

--	--

3. Did you lose consciousness? 0 1

MINUTES OR DAYS

--	--

--	--

IF YES - Specify how long.....

--	--

4. How old were you?

(INTERVIEWER: Code the age of the first episode with unconsciousness

if there has been more than one injury)

5. Specify injury:.....

.....
.....
.....

C. VISION DISTURBANCES:

Have you any vision problems? 0 1

Specify:
.....
.....
.....
.....

Since childhood, have you had one "lazy eye? 0 1

D. LEARNING DISABILITIES:

Did you have any learning problems at school? 0 1
(e.g.: trouble with learning, reading, writing, special education classes?)

IF YES, Specify:
.....
.....
.....
.....

E. ANAESTHETIC:

Have you ever had an anaesthetic? 0 1

IF YES:

How many general anaesthetics have you had?.....

--	--

Have you had any mood problems after an anaesthetic?..... 0

1

For how many of these anaesthetics did you have a mood problem
afterwards?.....

--	--

Specify:

.....

.....

.....

.....

.....

.....

Appendix I

Neuropsychological Testing - Bipolar Therapy Study

ID:

Date:.....

Handedness:

left right

Visual acuity:

good (no visual aids)

glasses

contact lenses

Years of secondary education:

1	2	3	4	5
---	---	---	---	---

Years of tertiary education:

1 2 3 4 5 5+

Specify tertiary:

Polytechnic

University

Other

Previous computer usage:

Yes

No

Level of confidence with computer use:

1 2 3 4 5

(none)

(high)

Any current medical illness:

Yes

No

Specify:.....

Medication and dose during week testing is conducted

	Medication	Dose
Medication #1		

Medication #2		
Medication #3		
Medication #4		
Medication #5		
Medication #6		

Add on if needed

Cigarettes/tobacco: **yes** **no** **No. per day:**

No. of years smoking:

No. of cups of caffeinated drinks per day:

Time started (Bireme & Faces): _____ **Time finished:** _____

Total time: _____

Time started (CANTAB & others) _____ **Time finished:** _____

Total time: _____

Tester: _____

Total length of testing: _____

Observations: _____

Appendix J

III ATTENTION DEFICIT DISORDER

This diagnosis is given to subjects who in childhood have manifested a persistent non-psychotic disorder characterized primarily by developmentally inappropriate short attention span, impulsiveness, and hyperactivity prior to age 18. Items are coded 1-5, in which a 4 or 5 represents "clinical significance". Thus, when considering a DSM-IV diagnosis of Separation Anxiety Disorder, do not view a symptom as present unless it is rated at least 4.

SCREENING QUESTION

When you were a child did you have trouble paying attention,
acting without thinking, or being too active? (0=No, 1=Yes)..... ☐

IF NO, SKIP TO OPPOSITIONAL SYMPTOMS

INATTENTION SYMPTOMS:

a. Failure to give close attention to details or makes careless mistakes

Fails to give close attention to details or makes careless mistakes in
schoolwork, work or other activities ☐

1 = No trouble giving close attention to detail or making mistakes

2 = Occasionally had fleeting trouble

3 = Occasional trouble

4 = Frequently didn't pay close attention to detail, or made careless mistakes

5 = Constantly didn't pay close attention to detail, or made careless mistakes

b. Difficulty sustaining attention in tasks or play activities

Did you have trouble paying attention or keeping your mind on
schoolwork or other tasks?

Even things you really like doing? Did your friends have the same trouble?

Were you worse than them?

When playing, could you usually stay with it for a while or did you find
you wanted to do something else before too long?

☐

1 = No problem paying attention to tasks

2 = Occasionally had fleeting trouble paying attention

3 = Occasionally had trouble paying attention

4 = Frequently had trouble paying attention

5 = Constantly had trouble paying attention

c. Often doesn't seem to listen

Did your mother (teacher) complain a lot that you weren't listening or that you
were daydreaming a lot? Often doesn't listen when spoken to directly

☐

1 = Nobody complained about not listening

2 = Occasionally didn't listen (no complaints

3 = Occasionally someone complained about not listening or daydreaming

4 = Frequently someone complained about listening

5 = Constantly had complaints about not listening

**d. How difficulty following through on instructions/often fails to finish things
he/she starts**

Did you have trouble following through when you are given something to do?

Did you have trouble finishing homework? ..Class assignments?

☐

Independent work? What kind of trouble was that?

1 = No trouble following through with tasks

2 = Occasionally had fleeting trouble following through

3 = Occasionally had trouble following through

4 = Frequently didn't follow through with tasks

5 = Constantly had trouble following through

e. Difficulty organizing tasks and activities

Did you have trouble doing things that had to be done in a certain kind of order,

☐

or that had a lot of different steps? Like what? Did you like to do models?

1 = No difficulty organizing

2 = Occasionally had fleeting trouble organizing

3 = Occasionally had trouble organizing work

4 = Frequently had trouble organizing work

5 = Constantly had trouble organizing work

f. Avoids, dislikes, reluctant to engage in tasks that require sustained mental effort

Often avoids, dislikes, or is reluctant to engage in tasks that require sustained

☐

mental effort (such schoolwork or homework)

1 = No problem

2 = Occasionally had fleeting trouble

3 = Occasionally had trouble

4 = Frequently had trouble

5 = Constantly had trouble

g Often loses things necessary for tasks or activities

Did you often lose things necessary for tasks or activities (e.g.: toys, school assignments, pencils, books, or tools) ☐

1 = No losing things

2 = Occasionally lost things

3 = Frequently lost things

4 = Constantly lost things

h Easily distracted

Did you find that almost anything could get your mind off the track of what you were doing? Did you get lost in the middle of a conversation? ☐
Often easily distracted by extraneous stimuli.....

1 = No problem with getting easily distracted

2 = Occasionally had fleeting trouble getting distracted

3 = Occasionally got easily distracted

4 = Frequently had trouble with getting easily distracted

5 = Had constant trouble getting easily distracted

i Often forgetful in daily activities

Often forgetful in daily activities ☐

- 1 = No problem
- 2 = Occasionally fleeting forgetful
- 3 = Occasionally forgetful
- 4 = Frequently forgetful
- 5 = Constantly forgetful

A.2 HYPERACTIVE SYMPTOMS:

a Often fidgets with hands or feet or squirms in seat

Did you often fidget with your hands or feet or wiggle in your seat?

(If adolescent) Do you always feel as though you want to be moving?

☐

Is it hard to sit still.....

- 1 = No trouble fidgeting
- 2 = Occasionally had fleeting trouble with fidgeting
- 3 = Occasionally had trouble fidgeting
- 4 = Frequently had trouble fidgeting
- 5 = Constantly had trouble fidgeting

a Difficulty staying seated

☐

Could you stay in your seat when you were supposed to?

- 1 = No trouble sitting still
- 2 = Occasionally had fleeting trouble sitting still
- 3 = Occasionally had trouble sitting still
- 4 = Frequently had trouble sitting still

5 = Constantly had trouble sitting still

b Runs about or climbs on things excessively

Were you always running around or climbing on things?

Often ran about or climbed excessively in situations in which it is
inappropriate (in adolescents or adults, may be limited to subjective
feelings of restlessness)

☐

1 = No trouble running about

2 = Occasionally had fleeting trouble running about

3 = Occasionally had trouble running about

4 = Frequently had trouble running about

5 = Constantly had trouble running about

c Has difficulty playing quietly

Did you have trouble playing or engaging in leisure activities quietly

☐

1 = No trouble playing quietly

2 = Occasionally had fleeting trouble playing quietly

3 = Occasionally had trouble playing quietly

4 = Frequently had trouble playing quietly

5 = Constantly had trouble playing quietly

d Always on the go or acts as if driven by a "motor"

☐

Were you always on the go?.....

1 = Not always on the go

2 = Occasionally had fleeting trouble being on the go

3 = Occasionally had trouble being on the go

4 = Frequently had trouble being on the go

5 = Constantly had trouble being on the go

e Often talks excessively

☐

Did you talk a lot more than other people?

1 = No trouble talking too much

2 = Occasionally had fleeting trouble talking too much

3 = Occasionally had fleeting trouble talking too much

4 = Frequently had trouble talking too much

5 = Constantly had trouble talking too much

A.2 IMPULSIVITY:

f Often blurts out answers to questions before they have been completed

☐

Did you often blurt out answers to questions before people finish asking?

1 = No blurting out answers

2 = Occasionally had fleeting trouble blurting out

3 = Occasionally blurted out answers

4 = Frequently blurted out answers

5 = Constantly blurted out answers

g Difficulty waiting for turn in games or group situations

Did you get into trouble because you couldn't always wait for your turn in games? Was that like your friends, or did you stand out?.....

☐

1 = No trouble waiting for turn

2 = Occasionally had fleeting trouble waiting for turn

3 = Occasionally had trouble waiting for turn

4 = Frequently had trouble talking too much

5 = constantly had trouble talking too much

h Often interrupts or intrudes on others

Did you often butt in on things other people are doing? Did they get annoyed? ..

☐

1 = No interrupting

2 = Occasionally had fleeting trouble with interrupting

3 = Occasionally interrupts

4 = Frequently interrupts

5 = Constantly interrupts

DSM-IV CRITERIA:

A. 6 inattention symptoms (rated a "4" or higher) OR 6 hyperactivity-impulsivity symptoms (rated a "4" or higher)	0	1
AND		
All symptoms present for at least 6 months	0	1
B. Some hyperactive-impulsive or inattentive symptoms that caused the impairment were present before age 7 years.....	0	1
C. Some impairment from the symptoms is present in two or more settings (e.g.: at school [or work] and at home).....	0	1
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning	0	1
E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mood disorder	0	1
DSM-IV CRITERIA MET: A, B, C, D and E answered "yes"	0	1

B EPISODE DESCRIPTION

Symptoms fit only when subject fit criteria for:

a. Major Depression (0=No, 1=Yes)

☐

.....

☐

b. Manic Disorder (0=No, 1=Yes)

.....

☐

c. Schizophrenia (0=No, 1=Yes).....

.....

C IMPAIRMENT

During the time you were feeling and behaving this way:

1 Sought help

☐

Did you or your parents look for help? (0=No, 1=Yes)

☐

Did you see someone for these problems? (0=No, 1=Yes).....

Who did you see?

2 Took medication

☐

Did you take medicine? (0=No, 1=Yes).....

What did you take?

D COURSE OF ATTENTION DEFICIT DISORDER (DSM IV)

1 Attention Deficit/Hyperactivity Disorder, Combined Type

if both Criteria A1 and A2 are met for 6 months

☐

(0=No, 1=Yes)

.....

☐☐

Age at onset of the disorder in years:

2 Attention Deficit/Hyperactivity Disorder, Predominantly Inattentive Type

☐

if Criterion A1 is met but Criterion A2 is not met (0=No, 1=Yes).....

.....

☐☐

Age at onset of the disorder in years:

3 Attention Deficit /Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type

☐

if Criterion A2 is met but Criterion A1 is not met

☐☐

Age at onset of the disorder in years:

.....